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THE CLINICAL USE OF SULPHANILAMIDE AND ITS DERIVATIVES IN THE TREATMENT OF INFECTIOUS DISEASES *

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INTRODUCTION

THE experimental observations [1, 2, 3, 4, 5, 6, 7] which have led to the use of sulphanilamide or its derivatives (chart 1) in the treatment of certain infectious diseases show that these chemicals have powerful chemotherapeutic effects in experimental infections. Clinical observations of their effects in human beings tend to confirm the laboratory results. In this communication we propose to discuss primarily the clinical application of these chemotherapeutic agents, and to detail the methods of their administration and the possible toxic effects which may become manifest in patients treated with sulphanilamide or its derivatives.

It is interesting to note that the first mention of these products in the medical literature was that of Foerster [8] who reported that " Streptozon " (Prontosil) had shown a marked chemotherapeutic effect in a boy suffering from a generalized staphylococcal infection. This report was delivered to the Düsseldorf Dermatological Society on May 17, 1933. In the following year Grutz [9, 10] reported that he had obtained good results in the treatment of toxic and septic erythemas by using " Prontosil " by mouth, and " Prontosil Solution " by the intravenous route. In the same year Veil [11] reported upon the use of " Prontosil Solution " in the treatment of " rheumatism."

Early in 1935 Gmelin [12] discussed the use of " Prontosil " and " Prontosil Solution " in the treatment of erysipelas in children and concluded that the results obtained were so satisfactory that extensive clinical trials were warranted. It is worthwhile to remember at this point that up until February 1935 no experimental data concerning "Prontosil " or " Prontosil

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Solution" had been reported. However, in that month, the first experimental report [1] was issued. It was accompanied by four more clinical papers dealing with the use of the dyes in various types of infectious processes.[13, 14, 15, 16] These clinical reports dealt with the use of "Prontosil" and "Prontosil Solution" in the treatment of streptococcal thrombophlebitis, adenitis, otitis media, erysipelas, puerperal fever and infectious arthritis. In general, the therapeutic results obtained were good. However, there was a divergence of opinion as to the efficacy of these chemicals in staphylococcal infections, Anselm [15] reporting favorable results, while Schreus [14] was doubtful of their value.

Following these reports there were numerous communications in the German literature dealing with the use of "Prontosil" and "Prontosil Solution" in a variety of diseases. Imhäuser [17] reported that he had obtained good results when these agents were used in the treatment of infections due to *E. coli*. Recknagel [18] believed that the chemicals were of value in pneumococcal and staphylococcal as well as streptococcal infections. Bingold [19] reported a patient with Hodgkin's disease, who either was cured or developed a prolonged remission after treatment with "Prontosil"! Einhauser [20] considered the drugs of great value in the treatment of sepsis, and Fuge [21] found that all cases of pure streptococcal puerperal sepsis recovered after treatment with the "Prontosils." In his opinion staphylococcal infections were not benefited.

Roth [22] found the drugs of value in hemolytic streptococcal infections, and Schranz [23] reported 60 patients ill with sepsis, treated with the "Prontosils," of whom 57 recovered. He advised that the chemicals be used as prophylactic agents before operative procedures in septic patients. Riecke [24] observed nine cases of purulent meningitis, all treated with these new compounds. Six of these cases had bacteria in cultures of their spinal fluid. Three of the nine patients recovered, but unfortunately, the author gave no data as to the spinal fluid findings in these patients. Scherber [25] used "Prontosil" in pemphigus vulgaris, and Kramer [26] reported good results from its use in 23 patients ill with erysipelas.

The first clinical report from France appeared in 1935. In that country, a product analogous to "Prontosil" called "Rubiazol" was being used. Vermelin and Hartemann [27] reported that they had treated patients with puerperal sepsis with "Rubiazol" by mouth and by the intravenous route since May 1935. Four of their patients developed severe reactions following the intravenous use of "Rubiazol" and one patient succumbed to the reaction. These observers considered the product with which they had been working as too toxic for further use. Following this report, Floch [28] described the good results that he had obtained in treating patients ill with tropical streptococcal lymphangitis with "Rubiazol." These patients were all treated with "Rubiazol" tablets by mouth. Lemièrre, La Porte, Laudat and Daum [29] carefully studied the effects of "Rubiazol" upon the kidney which had been damaged by an acute hemorrhagic nephritis. They con-

cluded the drug did not augment existing renal impairment. Meyer-Heine and Huguenin [30] studied the effects of the " Chlorohydrate of sulphamide-chrysoidine " in 150 patients ill with erysipelas. Eight of these patients were infants all of whom recovered. These observers noted no toxic effects and concluded that the chemical was a chemotherapeutic agent of great value. Recently Bloch-Michel, Conte and Durel [31] have reported that para-amino-benzene-sulphonamide and benzyl-para-amino-benzene-sulphonamide have shown very favorable therapeutic effects in the treatment of erysipelas. While para-amino-benzene-sulphonamide was effective, these authors preferred to use the benzyl derivative. Their results were striking as far as influencing the clinical course of the disease was concerned, and they reported no toxic effects from the use of the benzyl compound.

The first experimental and clinical report concerning the use of the " Prontosils " in England was that of Colebrook and Kenny [8] who, after preliminary tests in mice, applied these products to the treatment of puerperal fever. In a carefully studied series of patients they noted, not only a remarkable therapeutic effect in many cases, but an actual lowering of the expected case fatality rate. They stated that they had observed sulphemoglobinemia and mild renal irritation following the use of these drugs. Later, in a more extended clinical report [32] these observers concluded that the use of the " Prontosils " not only materially changed the clinical course of streptococcal puerperal infection, but also brought about a definite decrease in the expected case fatality rate. These two papers by Colebrook and Kenny have served to bring the possibilities of these new chemotherapeutic agents to the attention of the English speaking physicians.

Foulis and Barr [33] have recently described the beneficial effects of sulphanilamide in the treatment of puerperal sepsis. These observers used large doses of the chemical, and but one of their 28 patients, of whom 11 had a septicemia, succumbed to her infection. Their conclusions were that sulphanilamide had a marked chemotherapeutic effect and a low toxicity. Peters and Havard [34] used sulphanilamide in the treatment of 150 patients ill with scarlet fever. In the treated group, 35 per cent of the patients developed complications, while in an equally large parallel control group, 56 per cent of the patients developed complications. This difference in the complication rate was considered statistically significant. These observers noted but few toxic manifestations from the drug.

In a preliminary report Schwentker, Gelman and Long [35] noted that sulphanilamide had a definite therapeutic effect in the treatment of meningococcal meningitis, and concluded that results obtained with chemotherapy seemed quite as good as those obtained by the specific antiserum. Dees and Colston [36] have used sulphanilamide in the treatment of acute gonococcal urethritis and are " deeply impressed " with " the surprisingly prompt response to treatment " which they observed in the majority of their patients. Heintzelman and his associates [37] have recently reported favorable results

from sulphanilamide therapy in the treatment of a small series of Type III lobar pneumonia patients.

We [5, 38, 39, 40] have observed striking effects from the use of sulphanilamide and its dye derivatives in the treatment of experimental and clinical hemolytic streptococcal infections. Furthermore, we [40] pointed out, as did Rosenthal [42] and Cooper, Gross and Mellon [43] that sulphanilamide had some therapeutic effect in the treatment of pneumococcal infections in mice. Recently we [41] have observed that this chemical is effective in treating experimental *Cl. Welchii* infections in mice.

Thus, it seems that sulphanilamide, instead of being a chemotherapeutic agent specific for hemolytic streptococcal infections, is a drug possessing a broad chemotherapeutic valency. At the present time, enough experimental and clinical evidence exists to warrant the use of sulphanilamide or " Prontosil Solution " in the treatment of hemolytic streptococcal infections, and for the use of sulphanilamide in meningococcal infections. Its use in pneumococcal infection rests mainly upon experimental data which are not, as yet, conclusive. Clinical evidence alone supports the use of this chemical in gonococcal infections.

In evaluating the clinical effect of these new chemotherapeutic agents, in this report we will base our evidence solely upon the results obtained in the treatment of hemolytic streptococcal meningitis. It has been well recognized in the past [44] that this disease constituted an almost invariably fatal infection, with a case fatality rate of about 99 per cent. Hence, the reports of the case histories of patients recovering from this disease as the result of sulphanilamide therapy are of utmost importance in establishing the clinical value of sulphanilamide or its derivatives.

In 1936 Caussé, Loiseau and Gisselbrecht [45] reported the first patient ill with hemolytic streptococcal meningitis who, after treatment with " Prontosil," made a complete recovery. This was followed by the report of Arnold [46] who treated a patient suffering from hemolytic streptococcal meningitis with sulphanilamide. Recovery took place promptly. Since this first report Arnold [47] has successfully treated five additional patients ill with hemolytic streptococcal meningitis. Shortly after Arnold's report, Schwentker and his associates [48] reported recoveries in three out of four patients ill with hemolytic streptococcal meningitis and treated with sulphanilamide. Subsequent to these reports, Anderson [49] has reported one case of streptococcal meningitis, and Weinberg and his associates [50] two cases of the same disease who have recovered after being treated with sulphanilamide or its derivatives.

In this report we will discuss the course and therapy in four additional patients ill with hemolytic streptococcal meningitis.

Case Reports

Case 1. P. F., a seven year old white girl, was brought to the Harriet Lane Home of the Johns Hopkins Hospital in a comatose state on February 15, 1937.

Five weeks before entry into the hospital, she had had measles and a left ear ache. Four days before coming to the hospital, the child developed malaise, headache, fever and a left ear ache. Paracentesis of the left ear drum was performed and the ear discharged pus. On the day before entering the hospital, a headache and stiff neck appeared. Upon the morning of admission to Harriet Lane, the child was delirious and vomited. She became comatose while being brought to the hospital. The physical examination showed a comatose, moribund child. The pupils did not react to light, and there was a definite blurring of the nasal margin of the nerve head in the left eye. No mastoid swelling or stiffness of the neck could be elicited. Kernig's sign was negative. The remainder of the physical examination was essentially negative. Laboratory examinations: Urine, negative. Hemoglobin, 104 per cent Sahli; red blood cell count 5.4 millions; white blood cell count 38,200. Differential count, polymorphonuclears 45 per cent; juvenile polymorphonuclears 6 per cent; immature forms, 43 per cent; lymphocytes, 4 per cent. Cerebrospinal fluid, no increase in pressure; Pandy test 4 plus; white blood cells, 4,620; differential count, mononuclears 76 per cent; polymorphonuclears 24 per cent. Chains of gram positive cocci were seen in stained films of the cerebrospinal fluid. The Wassermann test was negative. Blood culture was negative. The culture of the cerebrospinal fluid showed a pure culture of Beta hemolytic streptococci. Cultures of the pus from the left external auditory canal showed Beta hemolytic streptococci, *Staphylococcus aureus* and *B. proteus*. Shortly after entry, 1.8 grams of sulphanilamide were administered by the parenteral route, and a transfusion of 80 c.c. of citrated blood was given. The patient died a few hours after entering the hospital.

Autopsy: "The longitudinal sinus is open. The brain is normal except that the meninges over the median portion of the base of the cerebellum, over the medulla and pons and extending up to the Sylvian fissure and optic chiasm show a whitish opacity. On section the ventricles are normal. The brain substance looks normal." Bacteriological cultures of the meninges showed Beta hemolytic streptococci.

Case 2. W. H., a nine year old white boy, was admitted to the Johns Hopkins Hospital on February 14, 1937, complaining of bilateral ear ache. Late in December 1936, the patient contracted a severe cold accompanied by pain in the right ear. Soon pain developed in the left ear, and a bilateral paracentesis was done. Then the ears drained profusely. Drainage continued until February 10, 1937, at which time a severe chill occurred and the patient became quite ill. Four days later, he came to the Johns Hopkins Hospital. His temperature at this time was 105° F. On physical examination a profuse, bubbly, pulsating discharge was noted in both external auditory canals, and both ear drums were found to be perforated. There was no mastoid tenderness. His neck was stiff and his hearing poor. A roentgenogram showed clouding of the right mastoid cells. A simple bilateral mastoidectomy was performed. Following the operation 1.6 grams of sulphanilamide were given by the subcutaneous route, and sulphanilamide tablets grains 5 q 4 hours were started. The culture of the pus from the mastoid region showed Beta hemolytic streptococci. The immediate postoperative course of this patient was favorable. Upon the tenth day after operation, the boy's temperature became definitely elevated. A roentgenogram did not show evidence of osteomyelitis. Because of a continuation of fever, the left mastoid region was again explored on February 27, and exuberant granulation tissue was removed. The lateral sinus appeared normal. The fever, however, continued. The sulphanilamide was increased to grains 10 q 4 hours. A sulphanilamide blood level of 9 milligrams per cent was reached and maintained. Because, however, of continuation of fever, the petrous portion of the left temporal bone was explored on March 11 and 27, 1937. Following the last operation the patient became nauseated, and the drug was discontinued on March 30. By April 1, only a trace of sulphanilamide was found in the blood. Stiffness of the neck was again noted on March 31. A lumbar puncture showed a cloudy fluid containing 5,950 white

blood cells. A culture of the spinal fluid showed Beta hemolytic streptococci. Intensive sulphanilamide therapy by the subcutaneous and intrathecal routes was begun on April 1. The details of this therapy are shown in chart 5. Despite all therapeutic efforts, the child died on April 8.

Autopsy: The gross specimen of the brain was described as follows: "The cerebral hemispheres show only a few little gray patches in the meninges. There are definite streaks of exudate along the fissures of Sylvius on each side. In the region of the cisterna magna, and over the inferior surface of the cerebellum, there is an extensive meningitis. The exudate extends up around the lateral and on to the dorsal surface of the pons. The lateral and third ventricles are a little widened, and contain a purulent exudate. On section no abscesses are found." Bacteriological cultures of the exudate yielded Beta hemolytic streptococci.

The method of therapy in this patient's case is shown in chart 1.

CHART I

Case 2

Date April 1937	Time of Treatment	Sulphanilamide Therapy (grams)			Cerebro-Spinal Fluid		Remarks
		Intrathecal	Subcutaneous	Per Os	W.B.C.	Culture	
1	4:30 p.m.	0.135	3.2			B.H.S.	150 c.c. 1/6 Molar Na Lactate Sc.
	11:45 p.m.	0.135	1.6		1,040	B.H.S.	
2	9:30 a.m.	0.16	2.4		120	B.H.S.	Blood Sulphanilamide = 10.3 mg. % C.S.F. Sulphanilamide = 11.1 mg. % CO_2 = 52 Vols. %. Hgb. 80%
	5:30 p.m.	0.24	2.4		8,200	B.H.S.	C.S.F. Sulphanilamide = 15.75 mg. % 150 c.c. 1/6 Molar Na Lactate Sc.
3	1 a.m.	0.16	2.4		1,048	B.H.S.	C.S.F. Sulphanilamide = 24.4 mg. %
	10:30 a.m.	0.32	2.4		650	B.H.S.	C.S.F. Sulphanilamide = 25. mg. %
	7 p.m.	0.28	1.6		508	B.H.S.	C.S.F. Sulphanilamide = 18.2 mg. %
4	3:00 a.m.	0.20	2.4		620	B.H.S.	C.S.F. Sulphanilamide = 16. mg. %
	11:30 a.m.	0.32		3.6	2,040	B.H.S.	Blood Sulphanilamide = 8.7 mg. %
	7:30 p.m.	0.28			1,180	B.H.S.	Transfusion 200 c.c.
5	3:00 a.m.	0.12			1,240	B.H.S.	C.S.F. Sulphanilamide = 10 mg. %
	11:30 a.m.	0.16		1.8	620	B.H.S.	Blood Sulphanilamide = 8 mg. %
	7:30 p.m.	0.12			636	B.H.S.	C.S.F. Sulphanilamide = 8 mg. %
6	3:30 a.m.	0.12	2.4			B.H.S.	C.S.F. Sulphanilamide = 13.7 mg. %
	1:00 p.m.	0.24	2.4	1.8		B.H.S.	C.S.F. Sulphanilamide = 11.25 mg. %
	8:30 p.m.	0.2	2.0		1,020	Neg.	C.S.F. Sulphanilamide = 16.25 mg. %
7	3:00 a.m.	0.12				B.H.S.	C.S.F. Sulphanilamide = 12 mg. % C.S.F. Sulphanilamide = 14 mg. %
	11:00 a.m.	0.12	2.0			B.H.S.	C.S.F. Sulphanilamide = 14 mg. % Blood Sulphanilamide = 11.2 mg. %
	8:30 a.m.	0.12	2.4		11,200	Neg .	150 c.c. 1/6 Molar Na Lactate Sc.
8	3:00 a.m.	0.12				B.H.S.	C.S.F. Sulphanilamide = 22.7 mg. %
	12:30 p.m.	0.16	2.			Neg.	C.S.F. Sulphanilamide = 14.1 mg. %
	7:45 p.m.						Hematocrit 40%. Icterus Index 15. Respiration ceased

Case 3. I. S. This 47 year old woman was a patient in the Spring Grove State Hospital, Maryland. Upon April 7, 1937, she was transferred to the hospital infirmary because the glands of her neck were swollen, and both ears were draining freely. Her subsequent course is shown in chart 2.

CHART II

Case 3

Date April 1937	Time of Treatment	Sulphanilamide Therapy (grams)			Cerebro-Spinal Fluid		Remarks
		Intrathecal	Subcutaneous	Per Os	W.B.C.	Culture	
8				0.3			Temp.: 103.6 to 104.6. 80 c.c. Prontosil solution s.c. Soda bicarb. 30 grains per os
9							Temp.: 99 to 104. No therapy. Both ears draining slightly
10				0.3			Temp.: 100 to 101
11							Temp.: 99.4 to 100. No therapy. Both ears draining slightly
12	5 p.m.	0.12			1900 P (a.m.) 3800 P (p.m.)	Strep. (smear only)	Temp.: 103 to 106. 40 c.c. Prontosil solution s.c. at noon. Blood culture = no growth
13	1 a.m. 10 a.m. 4 p.m. 5 p.m.	0.08 0.08 0.08	2.4 2.4 2.4	0.66	1630 P (a.m.) 1020 P (a.m.)	B.H.S. (33 cols.) B.H.S. (2 cols.)	Temp.: 102 to 104
14	1 a.m. 7 a.m. 10 a.m. 1 p.m. 5 p.m. 6 p.m. 9 p.m.	0.08 0.08 0.8 	2.4 2.4 2.4 	 1.3 1.3 1.3 1.3	1560 P (a.m.)	No growth	Temp.: 100 to 103. Soda bicarb. 40 grains per os
15	1 a.m. 8 a.m. 11 a.m. 1 p.m. 6 p.m. 9 p.m.	0.2 0.2 0.04 	 2.4 2.4 	1.3 1.3 1.3	2900 (a.m.) (P = 85% L = 10% M = 5%)	B.H.S. (6 cols.)	Temp.: 99.6 to 103.2. Soda bicarb. 10 grains per os
16	1 a.m. 8 a.m. 11 a.m. 1 p.m. 6 p.m. 8 p.m.	 0.12 0.12 	2.4 2.4 	 1.3 1.3 1.3	2360 (a.m.) P = 90% L = 8% M = 2%	No growth	Temp.: 100 to 103.4. Resp.: 28 to 52. Soda bicarb. 50 grains per os. CO_2 combining power, 24.8 vols. per cent at 6 p.m.
17	2 a.m. 9 a.m. 5 p.m. 9 p.m.	0.12 0.07 0.12 	2.4 2.4 	 1.3 1.3			Temp.: 101.2 to 105.6. Resp.: 36 to 60. $900\frac{M}{6}$ Na lactate at 4 p.m. Soda bicarb. 100 grains per os at 9 p.m. CO_2 combining power = 15.5 vols. per cent in the morning
18	1 a.m. 12 N. 2 p.m. 5 p.m. 10 p.m.	0.12 0.2 0.12	 	 1.3 1.3 1.3		No growth	Temp.: 99.4 to 102.6. Resp. 48 to 56. Soda bicarb. 250 grains per os. CO_2 combining power = 36.9 vols. per cent at 2:45 p.m.
19	8 a.m. 10 a.m. 2 p.m. 6 p.m.	 0.16 	 	1.3 1.3 1.3	775	No growth	Temp.: 100 to 102.8. Resp. 40 to 56. Soda bicarb. 150 grains per os. CO_2 combining power = 59.1 vols. per cent. Hgb. = 53%, R.b.c. = 2.6, W.b.c. = 21,000

P—Polymorphonuclear neutrophiles, L—Lymphocytes, M—Monocytes, B.H.S.—Beta hemolytic streptococci, s.c.—subcutaneously, Temp.—axillary temperature in degrees Fahrenheit.

CHART II—*Continued*

Date April 1937	Time of Treatment	Sulphanilamide Therapy (grams)			Cerebro-Spinal Fluid		Remarks
		Intrathecal	Subcutaneous	Per Os	W.B.C.	Culture	
20	8 a.m. 9 a.m. 10 a.m. 2 p.m. 6 p.m.	0.16		1.3 1.3 1.3 1.3	220 (a.m.)	No growth	Temp.: 99.6 to 100.8. Resp. 36 to 46. Soda bicarb. 150 grains per os. Hgb. = 49%, R.b.c. = 2.3, W.b.c. = 17,000
21	9 a.m. 11 a.m. 3 p.m. 10 p.m.	0.2		1.3 1.3 1.3			Temp.: 99.4 to 101.2. Resp. 32 to 48. Soda bicarb. 150 grains per os. Hgb. = 50%, R.b.c. = 2.3, W.b.c. = 24,000
22	10 a.m. 12 N. 1 p.m. 7 p.m. 8 p.m.	0.16		0.66 0.66 0.66 0.66			Temp.: 99 to 101.2. Resp. 34 to 42. Soda bicarb. 110 grains per os. Hgb. = 40%, R.b.c. = 2.4, W.b.c. = 19,000
23	1 a.m. 11 a.m. 8 p.m.			0.66 1.3 0.66			Temp.: 99 to 100.8. Resp. 32 to 36. Soda bicarb. 95 grains per os. Transfusion 600 c.c. citrated blood at 6 p.m.
24	10 a.m. 2 p.m. 10 p.m.			1.0 1.0 1.0			Temp.: 98.6 to 99.8. Resp. 20 to 38. Soda bicarb. 110 grains per os. Hgb. = 58%, R.b.c. = 3.1, W.b.c. = 15,700
25	9 a.m. 10 a.m. 3 p.m. 10 p.m.			1.0 1.0 1.0 1.0			Temp.: 98.2 to 99.8. Resp. 24 to 38. Soda bicarb. 40 grains per os
26	11 a.m. 6 p.m. 10 p.m.			1.0 1.0 1.0			Temp.: 99.2 to 100.2. Resp. 24 to 30. Soda bicarb. 150 grains per os. Hgb. = 65%, R.b.c. = 3.2, W.b.c. = 9200
27	1 p.m. 6 p.m. 10 p.m.	0.16		1.0 1.0 1.0	470	No growth	Temp.: 99.2 to 100.2. Resp. 28 to 36. Soda bicarb. 40 grains per os. CO_2 combining power = 59.1 vols. per cent. Hgb. = 67%, R.b.c. = 3.2, Retic. 7.6%, W.b.c. = 8000. Urine sterile
28	3 times a day			Total 3.0			Temp.: 98.8 to 99. Resp. 24 to 32. Soda bicarb. 40 grains per os
29	4 times a day			Total 4.0			Temp.: 99 to 100.6. Resp. 24 to 28. Soda bicarb. 40 grains per os
30	4 times a day			Total 4.0			Hgb. = 65%, R.b.c. = 3.2, W.b.c. = 7400
May 1–13	4 times a day			Total 4.0 per diem			Soda bicarb. 40 grains per os per diem
13–27	4 times a day			Total 3.0 per diem			Soda bicarb. 30 grains per os per diem
13							Hgb. = 60%, R.b.c. = 3.3, W.b.c. = 13,300

Case 4. J. E. B. Sydenham Hospital, Baltimore City Health Department. A three year old white boy entered the hospital on March 25, 1937, because of measles and pneumonia. His older brother and sisters had had measles. On March 18, the patient developed a cold, followed on the next day by a typical measles rash. Three days later, the child had difficulty breathing, a physician was called, and a diagnosis of pneumonia was made. The boy was removed to the hospital. Upon admission, he showed a fading measly eruption, no Koplik spots, and dullness and crepitant râles over the right lung field. Within a week after entry in to the hospital, the child had made a marked improvement. However, on April 7, his ears drained spontaneously, and a spiking fever appeared. This continued and because of a secondary anemia, he was given two transfusions of 100 c.c. of citrated blood on April 26

and 27. Just prior to the transfusions, on April 22, the child's red blood cell count was 3.2 millions, and his hemoglobin 52 per cent. He did not improve following the transfusions, and on April 26, it was noted that his neck was stiff. A lumbar puncture was performed, and gram positive diplococci were seen in the stained film of the cerebrospinal fluid sediment. The subsequent course of the patient is shown in chart 3.

CHART III

Case 4

Date April 1937	Sulphanilamide Therapy (grams)			Cerebro-Spinal Fluid		Remarks
	Intra-thecal	Subcu-taneous	Per Os	W.B.C.	Culture	
28	0.2	2.0		3750 75% Polys.	B.H.S.	Ears draining; culture = B.H.S. Neck stiff
29	0.23	3.0 2.0		2525 82% Polys.	B.H.S.	Neck stiff
30	0.2 0.2 0.2	2.0 3.0 3.0		1175 75% Polys.	Sterile	Able to bend neck
May 1	0.15	3.0 2.0		570 60% Polys.	Sterile	Markedly improved
2		2.0				Temperature normal upon 5/4/37
14				140 30% Polys.		Discharged from hospital 5/15/37

In reviewing the events in the histories of these four patients, it is evident that the first patient was moribund upon entry into the Harriet Lane Home and was beyond all therapeutic aid. The second patient represents a definite failure of sulphanilamide therapy for which we have no adequate explanation. It has been our experience that hemolytic streptococcal otitis media is very responsive to treatment with this chemical. This is also true of the postoperative course of patients ill with acute hemolytic streptococcal mastoiditis, in whom sulphanilamide therapy has been instituted. However, in this instance there was a definite progression of the streptococcal infection despite supposedly adequate therapy with sulphanilamide. Whether the discontinuance of the drug on March 30 permitted the streptococci to invade the spinal fluid is a matter of conjecture, but it is interesting to note that within 36 hours the first signs of meningitis appeared, and at that time less than 1 milligram per cent of sulphanilamide was present in the blood of the patient. However, the institution of adequate therapy did not influence the course of the disease despite the fact that the streptococci isolated from this patient were susceptible in vitro to the bacteriostatic effects of sulphanilamide.

The record of the third patient definitely demonstrates what may happen if therapy is discontinued too soon. In this instance, on the fourth day after treatment was stopped, the meningeal invasion took place. The effect of not adding base to the sulphanilamide therapy is also beautifully illustrated in this case, by the drop in the CO_2 combining power to 15.5 volumes per cent after 111 hours of treatment. Then with intensive alkali therapy, a normal CO_2 combining power was soon reëstablished.

The final case is of importance in showing the effect of neglecting specific therapy in the presence of a hemolytic streptococcal otitis media. This patient also illustrates the rapid and uneventful course to recovery that is being increasingly noted in hemolytic streptococcal meningitis since the introduction of sulphanilamide therapy.

In addition to these recorded cases of hemolytic streptococcal meningitis, we have been consulted in regard to nine other patients ill with this disease, eight of whom have recovered. Thus, from our own experience and that recorded in the literature, we have knowledge of 28 cases of streptococcal meningitis occurring within the last 16 months. All were treated with sulphanilamide or its derivatives. Twenty-four or 85 per cent recovered. This recovery rate is to be contrasted with a case fatality rate of 99 per cent before sulphanilamide therapy was used in hemolytic streptococcal meningitis. This constitutes irrefutable evidence of the value of sulphanilamide therapy in the treatment of severe Beta hemolytic streptococcal infections in human beings.

The Toxic Manifestations of Sulphanilamide and Its Derivatives

Sulphanilamide is a toxic chemotherapeutic agent, and its widespread employment will result in many fatalities unless the tendency towards its careless and reckless use is checked. Already fatalities attributed to the use of sulphanilamide or its derivatives have been reported [51] and we have seen one instance in which death was associated with a toxic effect of sulphanilamide.

The most serious toxic manifestations of sulphanilamide therapy are those associated with the blood or hematopoietic system. We have seen seven patients who developed acute hemolytic anemias characterized by a sudden fall in the hemoglobin and red blood cell count, and the appearance of macrocytosis, anisocytosis, poikilocytosis, elevated white blood cell counts, nucleated red blood cells and large numbers of reticulocytes in the peripheral blood. Six of the seven patients were definitely jaundiced, and in all a marked urobilinuria was present. All of these patients recovered promptly, but in five the anemia was so severe as to necessitate one or more transfusions.

The mechanism of the production of these anemias is as yet unknown, but it does not seem to be of the nature of a true idiosyncrasy because in two of the recovered patients the subsequent administration of test doses

of sulphanilamide did not result in any change in their red blood cells. Also, there has been no correlation between the amount of sulphanilamide administered and the development of anemia. It is probable that the anemias represent an abnormal susceptibility on the part of the red blood cells of certain individuals to severe hemolysis by sulphanilamide.

Another severe toxic effect of sulphanilamide has been the development of granulocytopenia. Plumer [52] has reported a patient who developed this toxic manifestation while under treatment with sulphanilamide. Despite the discontinuance of the drug, the patient died. In two instances Trumper [53] has seen definite leukopenias associated with a depression of the myeloid elements appear in patients who were being treated with sulphanilamide and " Prontosil Solution." We have seen one patient in whom death was associated with a granulocytopenia combined with a bilateral, lateral and cavernous sinus thrombosis. During the month before death, this patient had received irregular medication with " Prontosil Solution " and sulphanilamide. Recently, we have observed a patient who had made a rapid recovery from a gonococcal urethritis and arthritis as the result of sulphanilamide therapy. At the end of the third week of treatment he developed weakness, slight jaundice and a sore throat. Upon reëntry into the hospital he was found to have a mild anemia and a leukopenia associated with a marked depression of the myeloid elements. An extensive angina was present. No specific therapy was used and within 10 days the patient's blood picture was normal. He was then given two test doses of sulphanilamide, the first 0.3 gram, the second 2.0 gram by mouth, without showing any depression of his white blood cells. It seems, from this lack of response to the test dose, that the mechanism of the production of granulocytopenia by sulphanilamide differs from that by amidopyrine.

In addition to the severe toxic manifestations just described, sulphanilamide produces certain mild clinical toxic effects. In normal human beings, the ingestion of 50 grains of sulphanilamide is followed in six hours by slight dizziness and mild nausea. Ambulatory patients who are suffering from streptococcal or gonococcal infections often complain of dizziness, anorexia, nausea and sometimes of a sensation which is described as being similar to that experienced when mildly intoxicated with ethyl alcohol. These effects, however, are rarely noted in patients who are kept in bed during the period of therapy.

Practically every patient who receives sulphanilamide in therapeutic doses shows a fall in the CO_2 combining power of the blood. We have seen four cases of clinical acidosis, characterized by air hunger, and a very alkaline urine without ketonuria, which have developed in the course of sulphanilamide therapy. This toxic manifestation of the drug has been studied in the medical clinic of the Johns Hopkins Hospital by Southworth [54] who noted that a variable but consistent drop in the CO_2 combining power of the blood plasma occurred in 15 consecutive cases of streptococcal infec-

tion which had been treated with sulphanilamide. We have found that this fall in the CO_2 combining power of the blood plasma is associated with an absolute loss of sodium and potassium in the urine. This loss of base varies markedly in different individuals. Certain patients have a mechanism that permits them to control this loss of base before they develop a clinical acidosis. The exact method of the control of this excretion of base during sulphanilamide is under study at the present time. We have found that the administration of 10 grains of bicarbonate of soda with each dose of sulphanilamide is of value in preventing the fall in the CO_2 combining power, and at the present time we administer bicarbonate of soda routinely with each dose of sulphanilamide.

If acidosis should develop, the administration of 1/6 molar sodium lactate solution by the intravenous and subcutaneous routes is of definite value in combating this toxic manifestation of sulphanilamide therapy. In babies, frequent small hypodermoclyses of 1/6 molar sodium lactate solution may be used to prevent acidosis.

Sulphanilamide may cause fever. When this occurs, it is best to stop the drug for two or three days during which period the temperature will fall to normal if the fever is due to the sulphanilamide therapy.

We have carefully studied the urine of patients receiving sulphanilamide without noting signs of renal irritation. As we have stated previously, sulphanilamide is not excreted rapidly by the damaged kidney, and hence it tends to accumulate in the blood of patients having decreased renal functions. We believe that if the drug is to be used in patients with decreased renal function, the sulphanilamide blood levels should be followed daily. When the blood sulphanilamide level reaches 15 to 20 mg. per cent, the drug should be stopped.

Schwentker [55] and ourselves have noted morbilliform skin rashes accompanied by fever, which appeared in the course of sulphanilamide therapy. These rashes generally develop from the eighth to fourteenth day of treatment. When such skin eruptions develop, sulphanilamide therapy should be discontinued, and the rash and fever will disappear within 48 hours.

In patients suffering from the acute toxic manifestations of sulphanilamide therapy, we have found that large amounts of fluids act as an antidote. We have seen one patient who took 12 grams of sulphanilamide within 12 hours and who developed headache, dizziness, nausea and a moderate degree of cyanosis. Inasmuch as we know that the chemical is excreted with water, we had this patient force fluids to the extent of taking 5,000 c.c. of water by mouth within a six hour period. The drug was rapidly excreted, and after a few hours, all signs of toxicity disappeared.

Colebrook and Kenny [3] reported that the "Prontosils" had a mildly irritative effect upon the kidney, and that these compounds produced sulphemoglobinemia in three of their patients. They believed, however, that the association of saline cathartics with the therapeutic administration of the

" Prontosils " was a contributing factor in the production of the sulphemoglobinemia, and advised against the use of saline cathartics in patients receiving " Prontosil."

In our experience " Prontosil Solution " has produced but one toxic effect, namely, fever. This manifestation appears constantly in those normal subjects who have been tested with a single large dose (100 c.c.) given by the subcutaneous route. It also occasionally is seen on the third day or later of continuous " Prontosil Solution " therapy. It is our practice to discontinue " Prontosil Solution " if fever appears which is considerably out of proportion to the general clinical condition of the patient. As this generally occurs at a time when the streptococcal lesion is rapidly regressing, the clinical problem is not difficult. We have not seen any evidence of renal irritation in patients receiving " Prontosil Solution."

Methods of Administration of Sulphanilamide or Its Derivatives

Our experience leads us to believe that sulphanilamide per os is the drug of choice. If, however, the patient cannot swallow tablets, or oral administration of sulphanilamide is not desirable, we use either " Prontosil Solution " or an 0.8 per cent to 1 per cent solution of sulphanilamide in sterile physiological saline solution. These solutions are given parenterally by the subcutaneous route.

In our previous communication [5] we came to the conclusion based on our knowledge that a 1–10,000 concentration of sulphanilamide was definitely bacteriostatic in vitro, that this would constitute an effective therapeutic level in vivo. Our earlier system of dosage was, therefore, based upon amounts of sulphanilamide which would theoretically give us this concentration.

Recently, Dr. E. K. Marshall, Jr., and his associates [56, 57] have described a simple biochemical method for the quantitative determination of sulphanilamide in body fluid. They have noted, following a single oral dose in human beings, that the drug is absorbed in about four hours, and that a maximum concentration is reached in the blood stream within four to six hours. They demonstrated that the drug is almost wholly excreted in the urine, and that this is accomplished rapidly by the normal kidney. In patients with decreased renal function, Marshall found a diminished ability to excrete sulphanilamide, and noted that the continued ingestion of the chemical in these patients resulted in an accumulation of the drug in the body. It was also noted that the drug rapidly passed over into all body fluids in approximately the same concentration as was found in the blood. These observations have been of the greatest importance in establishing a rational basis for therapy in infected human beings.

Therefore, in patients ill with very severe infections, such as hemolytic streptococcal meningitis, peritonitis and septicemia, or in meningococcal meningitis or septicemia, we believe that because of the gravity of the prog-

nosis in such diseases, one should disregard all possible toxic effects of sulphanilamide or its derivatives in an attempt to control the infections as rapidly as possible. This we do by administering a large initial dose of sulphanilamide with the aim of attaining a blood level of 10 mg. per cent within four hours. In adult patients, i.e. those weighing 100 pounds or more, we administered an initial dose of from 10 to 16 five grain tablets. This initial dose should give a blood level of about 10 mg. per cent within four hours. Then, to maintain this level, we advise using three 5 grain tablets every four hours. If the patient weighs 50 to 90 pounds, the initial dose should be 6 to 10 five grain tablets followed by two or three tablets at four hour intervals. In children weighing from 25 to 50 pounds, four to six 5 grain tablets constitute the initial dose, followed every four hours by doses of one or two 5 grain tablets. Patients excrete the drug at slightly different rates, so the maintenance dose may vary somewhat.

We have found it advantageous to determine the blood sulphanilamide level four hours after the initial dose. If the blood does not show the expected level of 8 to 10 mg. per cent, this is evidence of faulty absorption, and the parenteral administration of the chemical should be instituted. It is of value to check the blood sulphanilamide level 24 hours after therapy has been started, to determine the adequacy of the maintenance dose of the drug.

The preparation of sulphanilamide for parenteral use is simple. This chemical is soluble up to 1 per cent in physiological saline solution at 37° C. It is our practice to bring the required amount of sterile physiological saline solution to a boil. It is then removed from the flame, and as soon as it stops boiling, 0.8 to 1 gram of sulphanilamide is added for each 100 c.c. of physiological saline solution. The hot saline solution is then agitated to facilitate the solution of the sulphanilamide, cooled to 37° C. and is administered by hypodermoclysis. A 1 per cent solution of the drug will remain fairly stable if kept at room temperature. If the temperature falls, or if the solution is placed in an ice box, the sulphanilamide crystallizes out of solution. It is our custom to make up the daily requirements of sulphanilamide solution for a patient each morning.

Our experience in the use of parenteral sulphanilamide solution leads us to believe that the following amounts represent adequate therapeutic doses. In adults, the initial hypodermoclysis should be 500 c.c. of a 1 per cent solution, followed by 300 c.c. at eight hour periods during the first 24 hours. The initial dose for individuals weighing from 50 to 90 pounds should be from 200 to 400 c.c. followed by 200 c.c. at eight hour intervals. Children weighing 25 to 50 pounds should receive an initial dose of 100 to 300 c.c. of sulphanilamide solution, this to be followed with 100 to 200 c.c. of the solution at eight hour intervals. In babies, it is difficult to determine the dose, but they should receive a total of 1 gram of sulphanilamide per 10 pounds of body weight during the first 24 hours.

Sulphanilamide solutions may be given by the intrathecal route in the treatment of streptococcal infections of the meninges. The drug has not been found irritating to the meninges, and the technic of administration is the same as that used in giving antisera by this route. The solution is warmed to 37° C. and after the spinal drainage has been completed, an amount of sulphanilamide solution equivalent to 5 or 10 c.c. less than the amount of cerebrospinal fluid which has been removed, is permitted to run into the spinal canal under the force of gravity. Never inject the solution under *positive pressure*. Intrathecal therapy may be given at eight hour periods in infections of the meninges.

" Prontosil Solution " should be given by the subcutaneous route. It is absorbed rapidly and is practically non-irritating. For two or three minutes after its injection, a sensation of burning or stinging may be noted at the site of injection. This may be obviated by infiltrating the area of injection with a small amount of a local anesthetic. The drug is absorbed rapidly, and has been noted in the urine within 15 minutes after a single subcutaneous injection of 100 c.c. of the solution. Because of the frequency with which the drug is given, we start its administration in the right pectoral region and proceed to the left pectoral region, then to the outside, top and inside of both thighs, and next to each of the buttocks. Following the injection in the buttocks, one may return to the right pectoral region.

In adults, the therapeutic dose of " Prontosil Solution " is 20 c.c. at four hour intervals or a total of 120 c.c. of the solution in 24 hours. Individuals weighing 50 to 90 pounds should receive from 10 to 15 c.c. of the drug at four hour intervals. Children weighing from 10 to 50 pounds should receive 5 to 10 c.c. every four hours. These doses should be continued in each instance until a definite clinical effect has been obtained. Then the dose may be gradually decreased. It will be noted that doses of " Prontosil Solution " such as we have recommended will color the skin pink and the urine bright red. " Prontosil Solution " is definitely irritating when given intrathecally, and should not be administered by this route. Severe reactions may occur after the intravenous administration of the drug.

After definitely favorable clinical effects in the patient have been obtained, the dose of sulphanilamide should be rapidly decreased. At first, the dose may be cut by one-third. Then if the improvement in the patient's condition is continued, the drug should be cut to one-third of the original amount. This should be continued until convalescence is well established.

Up to this point, we have discussed only the maximum dosage which is to be used in very severe streptococcal or meningococcal infections. Moderately severe streptococcal infections in adults may be controlled by the administration of three 5 grain tablets of sulphanilamide at four hour intervals. Mild streptococcal infections may be combated with one or two tablets at four hour intervals. In children, one or two tablets every four hours constitutes an effective dose. As soon as a definite clinical improvement is

noted, the amount of sulphanilamide should be decreased. If a recurrence of the infection occurs, or if clinical improvement is not seen after 36 hours of sulphanilamide therapy, the therapeutic dose of this substance should be increased.

Sulphanilamide can be used as a prophylactic agent in the prevention of streptococcal infections, especially in the face of epidemic outbreaks. In adults two 5 grain tablets three or four times a day constitute the prophylactic dose, while in children one tablet three times a day appears to be sufficient.

Summary

1. Clear experimental and clinical evidence is available which leads us to believe that sulphanilamide and its derivatives constitute powerful chemotherapeutic agents in the treatment of hemolytic streptococcal infections.

2. Experimental and clinical data support the use of sulphanilamide in meningococcal infections.

3. The clinical results obtained in treating gonococcal infections have been favorable.

4. Sulphanilamide has certain serious toxic effects upon the hematopoietic system.

5. The careless and reckless use of sulphanilamide is unwarranted, and will undoubtedly result in fatalities.

We wish to thank Dr. E. A. Park, Dr. Frances F. Schwentker and Dr. Herbert Harms for their courtesy in making the records of certain patients available to us.

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THE HEREDITARY FACTOR IN ESSENTIAL HYPERTENSION *

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EVEN before facilities were available for measuring the blood pressure it was observed that vascular disease occurred with unusual frequency among members of some families. In 1769, Morgagni recorded cases of apoplexy and said that he believed the condition was influenced by hereditary factors in these cases because many near relatives of the patients had been afflicted with a similar ailment. In 1872, Gull and Sutton reported a group of cases of chronic interstitial nephritis and expressed the opinion that the disease in these cases was due to an arteriocapillary fibrosis throughout the body rather than the result of a lesion in the kidneys. They commented on the hereditary nature of the disease in this group of cases. Janeway, in 1916, wrote: "The belief in an inherited quality of the arterial tissue with a tendency to premature death from apoplexy, angina pectoris and other local manifestations, is too firmly grounded in clinical observation to be without basis. Hypertensive arterial disease must be looked on to-day as the type in which heredity plays the largest rôle." These conclusions were derived mainly from scattered reports of human pedigrees and from casual clinical observations. It is only within the past 15 years that investigations of this problem have been of sufficient scope to be of significance.

The problem of the hereditary factor in hypertensive disease has been studied for the most part by three methods: (1) by observing and recording the histories of families in which vascular disease or hypertension has affected many members; (2) by investigating the family history as to the incidence of hypertensive cardiovascular disease among those who have or have had hypertension or a normal blood pressure; (3) by a study of the blood pressure of members of hypertensive and nonhypertensive families.

Weiss, Rosenbloom, Waldbott, Ayman and Étienne and Richard have studied the history of two or more generations of certain families in which an elevated blood pressure was found among a large number of the members. Ayman's report is especially significant as the blood pressure of three generations (32 members) of one family was measured.

Janeway obtained a history of familial cardiovascular disease from 50 per cent of a group of patients with hypertension. Popper studied 1,031 cases of hypertension and concluded that the hereditary factor was important. In studying the significance of an elevated blood pressure among young persons, Frost obtained a positive family history of cardiovascular disease from 28 per cent of 400 young adults who had an elevated blood pressure. Barach, in an especially detailed study of a small group of cases

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of hypertension obtained a family history of cardiovascular disease in 95 per cent. He called attention to the incomplete information obtained from the family histories taken in the routine manner. I have found this to be true and in many instances have secured additional information by detailed questioning. A general question as to whether the patient knows of any hypertension or cardiovascular disease among his relatives elicits poor information. A direct question concerning the state of the blood pressure, heart, kidneys and cerebrovascular system of each near relative will result in a surprising amount of additional information.

Data concerning the incidence of hypertensive cardiovascular disease among relatives of persons who have hypertension and relatives of persons who have a normal blood pressure are of more significance than are similar data concerning only the relatives of persons who have hypertension. O'Hare, Walker, and Vickers found that 68 per cent of 300 patients who had hypertension gave a family history of cardiovascular disease, as compared with 37 per cent of 564 patients who did not have hypertension. They concluded that heredity undoubtedly plays one of the most important rôles in the production of hypertensive disease. Glomset measured the blood pressure of 2,400 school children and found a positive family history among 39 per cent of the children who had an elevated blood pressure and among 10 per cent of the children who had a normal or low blood pressure.

Since medical information concerning relatives usually is incomplete, measurement of the blood pressure of relatives gives more reliable information than does a study of the family history. Weitz has measured the blood pressure of brothers and sisters of hypertensive and nonhypertensive persons. He found that the incidence of elevation of the blood pressure was significantly higher among siblings of persons who had hypertension than it was among siblings of persons who did not have hypertension. The most extensive and significant study of this type has been made by Ayman.[2] He studied the blood pressure of 1,524 members of 277 families and found that in the families in which both parents had absolutely normal blood pressures the incidence of elevated blood pressures among the children was only 3 per cent. In the families in which one parent had arteriolar hypertension the incidence rose to 28 per cent and in families in which both parents had arteriolar hypertension the incidence was 45 per cent. Ayman found that the so-called emotional hypertension of young adults occurred almost wholly among the children of hypertensive families. He confirmed Weitz' studies in regard to the higher incidence of elevated blood pressure among siblings of persons who had essential hypertension.

Rationale of Present Study

Previous investigations of the hereditary factor in essential hypertension have been unavoidably deficient because high blood pressure becomes evident at varying ages, usually in later adult life, and because many persons

who have essential hypertension have frequent periods during which the blood pressure will be found to be normal. The emotional stimulus of taking the blood pressure often is not sufficient to cause a maximal elevation of the blood pressure or to bring out a latent hypertension. This can be demonstrated by a comparison of the blood pressure obtained at the first examination and that taken after the application of a strong external, sensory stimulus, such as ice water. I have collected a group of 90 cases in which there were hypertensive changes in the retinal arterioles; in these cases the values for the blood pressure, which was taken in the office, were always less than 150 mm. of mercury for the systolic pressure and 95 mm. for the diastolic pressure and frequently were normal or low. On application of a cold stimulus the value for the blood pressure would increase from 20 mm. to 60 mm. of mercury higher than the readings taken in the office. In these cases, the emotional stimulus of taking the blood pressure is not sufficient to bring out a latent hypertension. In 608 cases I have studied the blood pressure before and during the application of a cold stimulus. In 43 per cent of the cases the values for systolic and diastolic blood pressures were 10 mm. of mercury higher during the application of the cold stimulus than they were on any reading before the application of the stimulus. In 8 per cent of the cases this increase amounted to 20 mm. or more of mercury. In 5 per cent of the cases the initial values were less than 120 mm. of mercury for the systolic pressure and less than 70 mm. for the diastolic pressure but the value for the systolic pressure increased to more than 145 mm. of mercury during application of the cold stimulus and the value for the diastolic pressure increased to more than 90 mm. Furthermore, it was found that from an emotional stimulus alone the elevation of blood pressure may be only in the systolic blood pressure, apparently as a result of cardiac stimulation rather than the result of vasoconstriction. Such emotional reactions of the blood pressure are of questionable significance if they are to be compared with the reactions in essential hypertension.

Hyperreactivity of certain portions of the arterial system is generally recognized as an important agent in producing the abnormality of the blood pressure which occurs in essential hypertension. A reliable method of measuring vasomotor reactivity, which does not depend on an emotional response and which would bring out a latent hypertension at each examination, should supply more complete information than has been obtained in previous studies of the hereditary factor in essential hypertension. The cold pressor test is believed to fulfill these requirements adequately.[9] The technic of the test is as follows: The subject is allowed to rest in a supine position in a quiet room for 20 to 60 minutes. Thirty minutes is a satisfactory rest period for persons who have a normal blood pressure. If hypertension is present, a longer period of rest may be necessary to establish a basal level. Several readings of the blood pressure are taken until a basal level has been approximated. The cuff of the sphygmomanometer is placed

on one arm of the subject and his hand is placed in ice water (4° C.) to a point just above the wrist. Readings of the blood pressure are taken at the end of 30 seconds and again at the end of 60 seconds. The maximal reading obtained while the hand is in the ice water is taken as an index of the response. The hand is removed from the ice water and readings are taken every two minutes until the blood pressure returns to its previous basal level. The maximal response frequently occurs within 30 seconds. The blood pressure of subjects who have a normal blood pressure returns to the basal level within two minutes. In the presence of established hypertension there

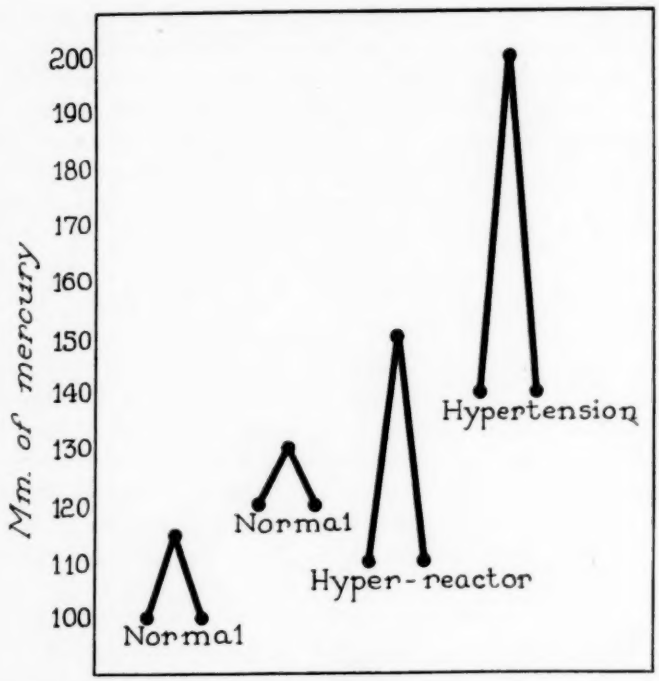

FIG. 1. Response of systolic blood pressure to cold pressor test.

may be a delay in the return of the blood pressure to the previous level. Sedatives and vasodilating drugs should not have been used by the patient for 24 hours before the test is performed. Observations have shown that the emotional factor does not play an important rôle in the response of the blood pressure to this test.*

The test has been used for five years in studying the reactions of the blood pressure of a large group of patients. It divides all persons into two groups: (1) Those who have minimal or "normal" reactions; and (2) those who have excessive or "abnormal" reactions. When the reactions to

* Unpublished data in thesis, "A Clinical Test of Vasomotor Irritability: Blood Pressure Response to Cold," by Edgar A. Hines, Jr. (1933), on file in The Mayo Foundation, The Mayo Clinic, Rochester, Minnesota.

the test were compared with the effects of environment, it appeared that the test is an index of the way in which a person's blood pressure reacts to environmental stimuli. Almost all persons afflicted with essential hypertension have abnormal or excessive reactions. One group of individuals who do not have hypertension gives excessive reactions to the cold pressor test in both systolic and diastolic blood pressure. These individuals have been called " hyperreacting normals " (figure 1). In a study of 400 school children, 18.7 per cent were found to be hyperreactors to the test.[8] It is believed that this hyperreacting state of the blood pressure of normal persons represents a prehypertensive stage of essential hypertension and that many of these persons eventually will have essential hypertension. The transition from this hyperreactive state to essential hypertension has been observed among a small number of individuals during the five-year period of observation. Because of these significant observations concerning the cold pressor test, I have used the test in a study of the hereditary factor in vasomotor reactivity and in essential hypertension.

Method of Study

The observations have been carried out along three lines: (1) a correlation of the type of reaction to the test and the incidence of hypertensive disease in the family history; (2) a study of the reaction of twins to the test; (3) a study of the reaction of members of hypertensive and nonhypertensive families to the test.

Data

Correlation of the Type of Reaction and the Family History. A detailed study was made of the incidence of hypertensive cardiovascular disease among relatives of 492 " normal reactors " and 116 " hyperreactors." The results were compared with the family history of hypertensive cardiovascular disease in a group of 267 cases of essential hypertension. The results are shown in table 1. From this table, it may be seen that a positive

Table I

Incidence of Hereditary Factor Among Hypo- and Hyperreactors and Patients with Essential Hypertension

	Number	Family history of hypertensive cardiovascular disease, per cent
Subjects with a normal blood pressure:		
Hyporeactors	492	17.2
Hyperreactors	116	84.2
Subjects with essential hypertension	267	86.6

family history of hypertensive cardiovascular disease is five times more frequent among hyperreacting normals than it is among persons who have a

normal blood pressure and give a normal reaction to the cold pressor test. Also, there is a close correlation between the incidence of an hypertensive cardiovascular family history among patients who have essential hypertension and persons who belong in the hyperreacting normal group.

The Blood Pressure Reaction of Twins. Seven sets of identical twins and three sets of fraternal twins have been tested. In all of the sets of identical twins the response of one twin to the cold pressor test was similar to that of the other twin, whereas, in two of three sets of fraternal twins, the response was different (figure 2). One of the sets of identical twins

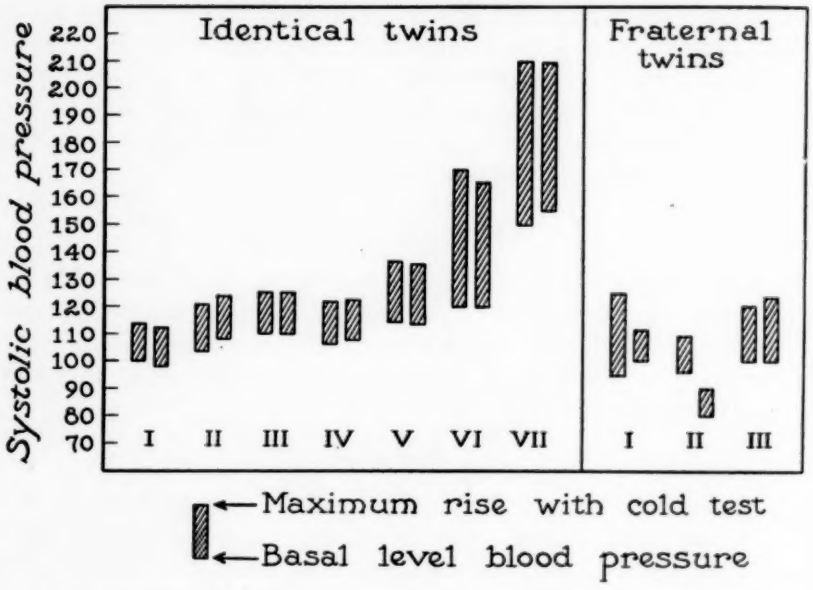

FIG. 2. Response of the blood pressure of twins to the cold pressor test.

had essential hypertension. Their basal blood pressure readings and response to the test were almost identical.

The Reaction of the Blood Pressure and Presence of Hypertension Among the Members of Hypertensive and Nonhypertensive Families. Thirty families, consisting of 256 members, are included in this group. In 12 of these families there was no evidence or history of hypertensive cardiovascular disease; in 18 families there was a definite hypertensive diathesis. Blood pressure readings were made and a cold pressor test was performed on every available living member of each family and a careful inquiry was made as to the cause of death of deceased near relatives. The pedigrees of some of these families are shown in figures 3, 4, 5, and 6. In the family group shown in figure 6, I was able to make blood pressure readings and make the test on every living member of the group, which consisted of 57 members, or three generations.

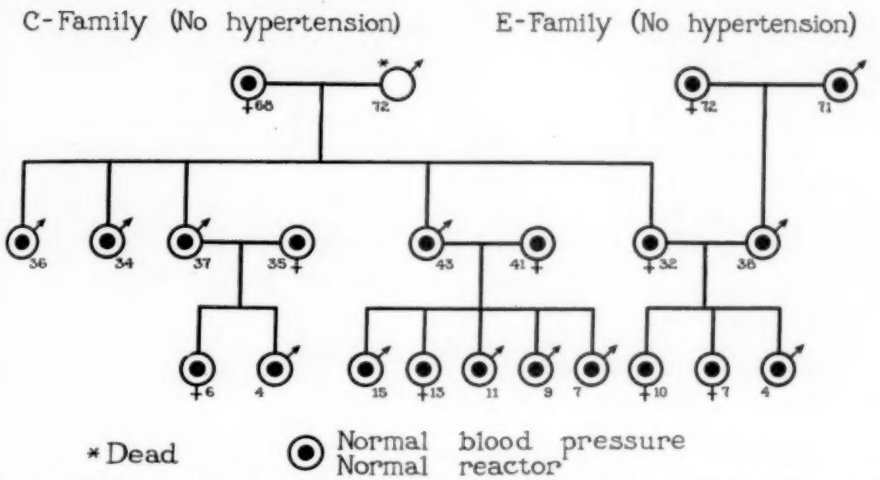

FIG. 3. Family tree showing blood pressure and response of blood pressure to cold test in nonhypertensive families.

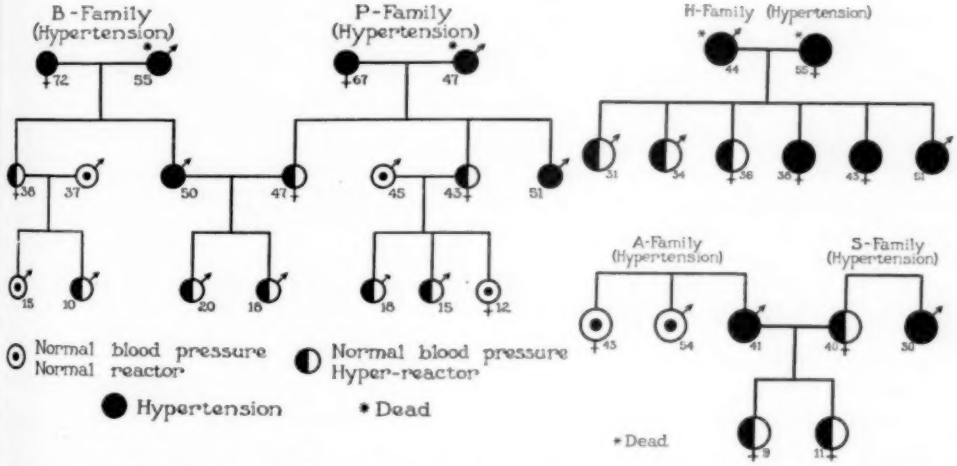

FIG. 4. Family trees showing blood pressure and response of blood pressure to cold pressor test in hypertensive families.

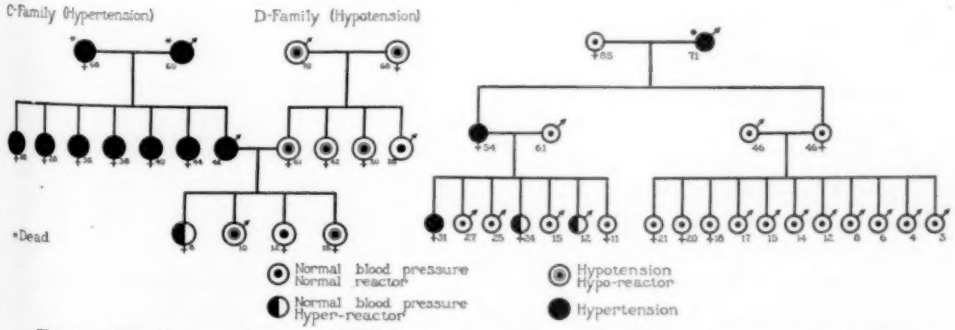

FIG. 5. Family trees showing blood pressure and response of blood pressure to cold pressor test in hypertensive and nonhypertensive families and in a family in which hypotension was present.

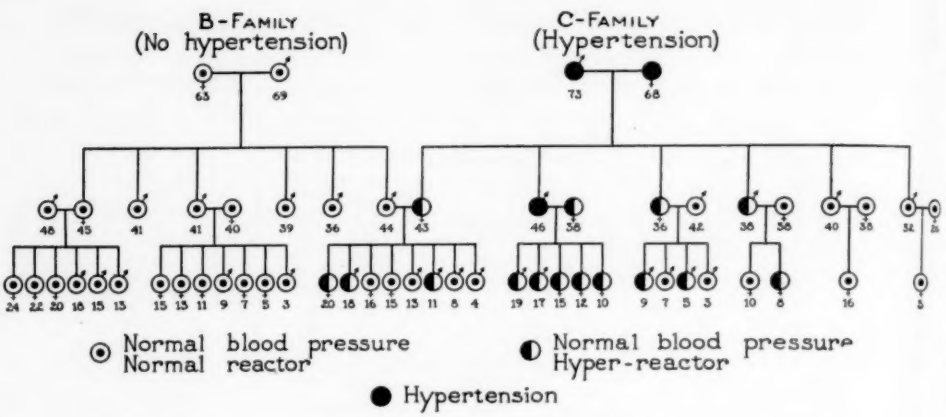

FIG. 6. Family tree showing blood pressure and response of blood pressure to cold pressor test in hypertensive and a nonhypertensive family.

Investigation of these data revealed that when both parents had a normal blood pressure and were normal reactors, all of the children were normal reactors. If both parents had hypertension or were hyperreacting normals, 95 per cent of the children had hypertension or were hyperreactors to the test, and if one parent had hypertension or was a hyperreactor and the other parent was a normal reactor, 43.4 per cent of the children were hyperreactors or had hypertension. In three families of two generations, the parents had essential hypertension or had died of it and all of the children had hypertension or were hyperreactors.

Summary and Conclusions

The hereditary factor in essential hypertension has been considered. Data have been presented regarding the reaction of the blood pressure to a standard stimulus (cold pressor test) in 608 cases in which the blood pressure was "normal," in 10 pairs of twins, and in 256 members of 30 hypertensive and nonhypertensive families. A study has also been made of the family history of the 608 individuals who had a normal blood pressure and of 267 individuals who had essential hypertension. A positive family history of hypertensive cardiovascular disease is five times as frequent among individuals who have hypertension or who are hyperreactors to a standard stimulus test than it is among individuals who react normally to the test. In the study of the twins and the family groups it was found that the type of blood pressure reaction to the test followed an inherited pattern. Inasmuch as I so far have not found any hyperreactor who did not have one parent who had hypertension or was a hyperreactor, it is probable that the trait is inherited as a dominant characteristic. The excessive or "hypertensive" type of reaction occurred predominantly among members of families in which there was an hypertensive diathesis. These findings are considered

to be strong evidence that the hereditary factor plays an important rôle in the development of essential hypertension. The inherited quality may be a vasomotor system which reacts excessively to certain external and internal stimuli and eventually results in the development of essential hypertension in many cases.

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FACTORS INFLUENCING THE PROGNOSIS IN DIABETIC COMA *

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In making this report we have two purposes, first to present briefly chemical and clinical data of cases of diabetic acidosis as encountered in a large city hospital, and second to evaluate data determined at admission in regard to their effect on the prognosis.

For many years we have been impressed with the fact that both the rate of incidence and the mortality rate of acidosis are much higher in diabetics of the economic and intellectual class of society which is dependent on the city hospital than in those diabetics seen in private practice. During the six years 1931 to 1936 there were admitted to the wards of the Metabolic Division, Philadelphia General Hospital, 3009 cases of diabetes; 268 of these patients were admitted in acidosis and it is their records which form the material of this report. There were 224 individuals, as 21 patients were admitted in acidosis 44 additional times. Eleven patients were admitted in acidosis twice, four patients three times, four patients four times, one patient five times, and one patient ten times. The latter patient (No. 252) was given a job in the hospital nearly two years ago and has not been in coma during this time.

The Metabolic Division has its own trained personnel and physical equipment, consisting of two wards of 25 beds each, laboratories, diet kitchen and out-patient department, all located as a single unit. All the diabetics of the hospital are concentrated in this department regardless of complications, except cases of open tuberculosis and psychopathic patients. Without this department the diabetic patients would be scattered among ten medical services, four surgical services and numerous special services. The out-patients consist only of patients who have been discharged from the wards. As a result of the above circumstances a new patient usually is one who has come to the hospital only because of some serious complaint or complication, and who knows little or nothing about diabetes, and about whom the staff has no information. Of the 224 individual patients in this report, 82 patients did not know they had diabetes at the onset of the acidosis which caused them to be admitted to the hospital.

In a large series of uncontrolled diabetics, all degrees of acidosis occur and it is difficult to decide which cases are worthy to be included in a report. Some authors give no criteria concerning the basis of selection of the cases included in their reports. More usually the authors have selected some figure for the CO_2 volume per cent and included all cases below that figure.

* Presented at the St. Louis meeting of the American College of Physicians, April 22, 1937.

The figures selected have varied widely, ranging from 15 [1] to 45.[2] Joslin [3] in his seven reports has included cases of 20 and below. In this report all cases have been reported in which the CO_2 volume per cent was 29 or lower. The reasons for selecting this figure will be discussed later in this report.

Of the 268 cases admitted in acidosis 117 died, a mortality of 43.7 per cent. Some years ago, when it became obvious to us that our mortality was much larger than that reported from other clinics, we made a careful study of our records for the purpose of analyzing the causes of the high mortality and with the hope of reducing it. Because of the large number of patients having serious complications, we found it necessary to separate the cases into groups and the criteria which we set up were as stated in table 1.

TABLE I

Criteria Used to Group the Diseases Complicating Diabetic Acidosis

A. No complicating disease (cases recovering = AR; cases dying = AD).
B. 1. Any disease sufficient to precipitate coma in a diabetic, but not severe enough to cause death as a rule in a non-diabetic.
2. Any disease severe enough to cause considerable mortality in non-diabetics. If the case of acidosis dies, he has been out of acidosis less than 48 hours prior to death (cases recovering = BR; cases dying = BD).
C. 1. Like B_2, except that all cases die, but have been out of acidosis more than 48 hours prior to death.
2. Any disease the mortality of which would be very high in non-diabetics in a short period of time. The acidosis is merely a terminal event of the fatal disease.
3. Any disease from which the patient dies many days after complete recovery from the acidosis.

It will be noted that the certainty of a patient's having died from the complication and not the acidosis increases progressively from B_1 to C_3 in this table. In general the " A " cases had no complications, the " B " cases had complications but when death occurred the chief factor was probably the acidosis, and the " C " cases all died, the complications being of such severity that all would probably have died even if there had been no acidosis.

We have included as complications only such conditions as were likely to precipitate acidosis. General conditions such arteriosclerosis, latent syphilis, etc., are not included regardless of what effect they may have had on the general vitality of the patient. We have not regarded anuria as a complication, but as a condition directly dependent upon the acidosis.

There were 129 uncomplicated cases and 139 cases with complications. In the " A " group (tables 2 and 3) 97 recovered and 32 died, the mortality being 24.8 per cent. In the " B " group (tables 4 and 5) 54 recovered and 27 died, the mortality being 33.3 per cent. In the " C " group (table 6) all 58 cases died, of which, however, 19 cases died many days after recovery from the acidosis. In tables 7 to 15 the letters " AR " refer to cases recovering in the " A " group, " AD " to cases dying in the " A " group, " BR " to cases recovering in the " B " group, " BD " to cases dying in the " B " group, " C_1C_2 " and " C_3 " to cases as set forth in table 1, " R " to total cases recovering and " D " to total cases dying, following which the mortal-

TABLE II

PHILADELPHIA GENERAL HOSPITAL

Diabetic Acidosis with No Complications. Cases Recovering (AR)

	Patient No.	Age	Sex	Color	Date Admitted	Blood Findings on Admission				On Admission		
						Sugar mg. %	CO_2 vol. %	Urea N mg. %	W.B.C. thous.	Mentally	Duration Acidosis	Known Diabetic
1.	12	21	F	B	1/ 6/31	348	24	13	9.7	C	3	Yes
2.	120	16	F	W	4/10/31	328	14	16	14.0	U	4	No
3.	124	29	F	W	4/14/31	576	21	18	—	C	—	Yes
4.	132	8	F	W	4/18/31	400	18	12	18.9	C	1	Yes
5.	12	22	F	B	4/21/31	350	22	13	10.4	C	2	Yes
6.	165	48	F	B	5/20/31	568	12	34	22.9	C	—	No
7.	12	22	F	B	6/11/31	348	25	10	—	C	3	Yes
8.	211	19	F	B	7/20/31	480	13	9	21.7	C	3	Yes
9.	254	26	M	B	8/27/31	410	21	10	5.5	C	—	Yes
10.	254	26	M	B	12/ 2/31	348	20	15	—	C	2	Yes
11.	348	30	M	B	12/24/31	720	24	65	—	C	—	No
12.	368	15	F	W	1/ 6/32	320	27	11	—	C	2	Yes
13.	408	21	F	W	2/15/32	464	14	18	21.5	C	—	—
14.	415	11	M	B	2/23/32	304	20	18	—	C	3	No
15.	427	26	F	W	3/17/32	608	14	17	29.4	U	—	No
16.	492	13	M	W	5/14/32	344	17	10	—	C	—	Yes
17.	252	17	M	B	5/10/32	280	20	14	21.6	C	2	Yes
18.	79	23	M	W	7/13/32	364	22	11	5.6	C	4	Yes
19.	132	9	F	W	7/17/32	480	18	14	20.4	C	3	Yes
20.	132	9	F	W	7/27/32	324	22	12	4.4	C	1	Yes
21.	588	24	F	W	9/ 9/32	340	24	14	—	C	3	Yes
22.	590	10	F	W	9/10/32	280	20	10	—	C	3	Yes
23.	120	18	F	W	9/28/32	320	17	11	17.6	C	1	Yes
24.	252	17	M	B	10/ 4/32	400	21	22	14.0	C	—	Yes
25.	390	28	M	W	10/11/32	388	17	12	42.6	C	2	Yes
26.	415	12	M	B	11/ 4/32	290	23	12	—	C	—	Yes
27.	658	20	F	W	11/12/32	462	16	20	29.5	C	3	Yes
28.	688	25	M	B	12/14/32	290	13	12	—	C	4	Yes
29.	252	17	M	B	1/ 5/33	556	11	21	13.8	C	4	Yes
30.	716	52	F	W	1/10/33	286	26	13	—	C	—	Yes
31.	723	38	F	W	1/18/33	236	23	26	—	C	2	—
32.	739	38	F	W	1/28/33	434	27	27	—	C	1	Yes
33.	252	17	M	B	2/ 6/33	396	19	18	24.8	C	—	Yes
34.	658	21	F	W	3/15/33	610	14	15	—	U	2	Yes
35.	120	18	F	W	3/20/33	316	20	11	14.5	C	1	Yes
36.	20	11	M	W	4/ 2/33	337	15	11	—	C	1	Yes
37.	890	29	F	B	6/11/33	414	16	15	—	C	4	Yes
38.	861	23	M	W	7/ 5/33	720	18	19	17.0	C	3	Yes
39.	423	28	F	W	7/ 9/33	448	17	14	19.8	C	—	Yes
40.	946	43	F	B	8/ 6/33	580	12	30	23.5	U	4	Yes
41.	963	48	F	B	8/23/33	384	24	24	—	C	—	Yes
42.	977	52	F	W	9/10/33	464	18	41	—	C	2	Yes
43.	252	18	M	B	10/ 2/33	655	22	18	23.5	C	2	Yes
44.	1038	38	F	B	11/ 7/33	806	16	28	18.8	U	4	Yes
45.	897	28	F	B	1/12/34	150	19	12	—	C	3	Yes
46.	1128	16	F	W	3/ 7/34	346	25	9	9.8	C	—	Yes
47.	1253	54	F	W	6/28/34	624	27	18	—	C	—	No

TABLE II—*Continued*

	Patient No.	Age	Sex	Color	Date Admitted	Blood Findings on Admission				On Admission		
						Sugar mg. %	CO_2 vol. %	Urea N mg. %	W.B.C. thous.	Mentally	Duration Acidosis	Known Diabetic
48.	252	19	M	B	7/ 4/34	464	10	16	—	C	3	Yes
49.	252	19	M	B	9/10/34	388	16	17	13.2	C	4	Yes
50.	415	13	M	B	9/10/34	300	26	13	14.3	C	1	Yes
51.	128	20	M	W	9/20/34	468	23	21	28.4	C	2	Yes
52.	1128	16	F	W	10/ 8/34	320	11	12	22.6	C	4	Yes
53.	178	18	F	W	10/18/34	400	24	12	—	C	3	Yes
54.	875	39	M	B	10/31/34	324	27	11	10.6	C	3	Yes
55.	1396	11	F	B	11/30/34	352	20	14	20.3	C	4	Yes
56.	1404	57	M	W	12/10/34	756	13	12	48.3	C	1	Yes
57.	848	20	M	W	1/ 6/35	904	15	30	17.5	C	3	Yes
58.	1440	39	F	B	1/20/35	1024	15	63	19.3	U	1	No
59.	1450	16	F	B	1/30/35	680	13	19	20.3	U	3	No
60.	1463	38	F	B	2/ 5/35	708	12	15	20.0	C	1	No
61.	252	20	M	B	2/27/35	808	12	30	54.7	C	2	Yes
62.	1511	22	M	B	3/20/35	1056	14	43	27.5	C	4	No
63.	1519	42	F	W	3/29/35	612	12	35	41.5	U	3	Yes
64.	252	20	M	B	5/ 6/35	800	14	35	36.9	C	3	Yes
65.	1608	42	F	B	6/18/35	992	19	38	17.8	C	4	No
66.	1450	16	F	B	6/25/35	480	16	10	23.1	C	3	Yes
67.	1671	16	F	W	8/21/35	296	22	23	7.9	C	—	No
68.	1685	48	F	B	9/ 6/35	848	11	21	24.2	C	2	No
69.	1450	16	F	B	9/ 6/35	352	14	11	18.5	C	4	Yes
70.	1543	46	F	W	9/ 9/35	912	11	34	21.5	C	3	Yes
71.	1474	13	F	W	10/15/35	374	14	15	25.3	C	—	Yes
72.	1748	21	F	W	11/ 2/35	320	18	16	12.6	C	4	No
73.	1788	51	F	W	12/ 8/35	600	13	22	45.9	U	2	Yes
74.	1808	52	M	W	1/ 3/36	600	22	65	11.0	C	4	Yes
75.	1689	42	F	W	1/11/36	560	25	16	12.5	C	1	Yes
76.	307	59	F	W	1/12/36	1080	15	75	17.0	C	1	Yes
77.	1820	52	F	W	1/21/36	262	25	18	—	C	4	No
78.	848	22	M	W	2/ 7/36	680	25	28	23.5	C	4	Yes
79.	1193	23	F	W	2/18/36	384	24	13	—	C	—	Yes
80.	1474	13	F	W	3/13/36	368	17	12	—	C	—	Yes
81.	1881	43	F	W	4/ 4/36	732	13	30	19.3	U	2	Yes
82.	1882	60	F	W	4/ 4/36	300	23	17	—	C	2	Yes
83.	1827	14	F	W	4/ 4/36	608	14	16	72.1	C	—	Yes
84.	1474	13	F	W	4/18/36	464	22	21	32.2	C	1	Yes
85.	1936	73	F	B	6/ 8/36	372	29	21	11.0	C	1	Yes
86.	964	45	F	B	6/11/36	204	25	10	—	C	4	Yes
87.	614	45	M	W	8/ 8/36	1168	17	55	15.1	C	—	Yes
88.	1827	14	F	W	8/31/36	296	19	14	18.0	C	—	Yes
89.	2001	39	M	B	9/ 2/36	415	25	45	—	C	2	Yes
90.	2032	12	M	W	9/30/36	800	19	27	51.0	C	1	Yes
91.	2036	32	M	B	10/ 2/36	440	18	14	—	C	3	Yes
92.	1827	14	F	W	10/14/36	366	26	13	22.6	C	—	Yes
93.	807	40	F	W	10/31/36	270	14	17	11.5	C	3	Yes
94.	1827	14	F	W	12/10/36	366	23	15	27.5	C	—	Yes
95.	193	15	M	W	12/12/36	310	14	10	25.5	C	2	Yes
96.	2096	22	M	W	12/22/36	300	25	14	11.5	C	4	Yes
97.	72	14	F	W	12/31/36	484	9	16	42.6	C	2	Yes

TABLE III

PHILADELPHIA GENERAL HOSPITAL

Diabetic Acidosis with No Complications. Cases Dying (AD)

	Patient No.	Age	Sex	Color	Date Admitted	Blood Findings on Admission				On Admission			Post Mortem	Time Lived
						Sugar mg. %	CO_2 vol. %	Urea N mg. %	W. B. C. thous.	Mentally	Duration Acidosis	Known Diabetic		
1.	14	52	F	W	1/10/31	404	12	70	22.1	C	3	Yes	p.m.	9 hrs.
2.	106	56	F	W	3/26/31	600	22	53	8.7	C	3	Yes	—	6 hrs.
3.	145	37	F	W	4/14/31	576	15	20	16.8	U	1	No	p.m.	12 hrs.
4.	32	16	F	W	3/21/32	728	14	18	45.5	U	2	Yes	—	9 hrs.
5.	535	35	F	B	7/ 5/32	752	19	60	—	U	3	No	p.m.	6 hrs.
6.	186	15	F	W	8/12/32	424	12	10	—	U	3	Yes	—	11 hrs.
7.	589	65	F	W	9/10/32	960	15	75	20.9	U	4	Yes	—	11 hrs.
8.	666	22	F	B	11/23/32	450	18	22	10.5	U	4	No	—	12 hrs.
9.	973	45	M	W	9/ 6/33	728	12	23	14.5	U	1	Yes	p.m.	24 hrs.
10.	988	25	F	W	9/21/33	770	14	30	29.8	U	3	Yes	p.m.	14 hrs.
11.	1006	56	F	W	10/ 7/33	808	21	—	—	U	3	Yes	—	3 hrs.
12.	1113	50	F	B	2/14/34	740	23	90	5.8	U	—	No	p.m.	15 hrs.
13.	1173	21	F	W	4/17/34	368	12	22	—	U	4	No	p.m.	18 hrs.
14.	1227	53	F	B	6/10/34	1028	12	—	—	U	3	No	—	3 hrs.
15.	1250	30	M	B	6/26/34	770	17	—	—	C	4	No	—	7 hrs.
16.	1267	30	M	W	7/17/34	428	11	—	—	U	3	No	p.m.	7 hrs.
17.	1295	35	F	W	8/10/34	720	13	40	—	U	4	Yes	p.m.	10 hrs.
18.	1296	51	F	W	8/12/34	386	14	14	22.4	C	4	No	—	15 hrs.
19.	1325	38	M	B	9/18/34	682	10	65	15.3	U	4	No	p.m.	3 hrs.
20.	86	40	F	W	10/ 9/34	1000	7	20	31.6	U	2	Yes	—	16 hrs.
21.	1347	52	F	W	10/15/34	568	26	57	24.9	U	4	Yes	—	4 hrs.
22.	1439	25	F	W	1/19/35	370	28	27	6.1	C	2	No	—	8 hrs.
23.	1566	46	M	W	5/ 8/35	200	27	43	12.6	U	3	Yes	p.m.	26 hrs.
24.	1576	36	M	B	5/16/35	1256	18	78	11.8	U	2	No	p.m.	2 hrs.
25.	1594	12	M	W	5/31/35	960	14	22	23.4	U	1	No	p.m.	21 days
26.	1706	50	F	W	9/29/35	500	14	34	10.6	U	3	No	p.m.	7 hrs.
27.	1555	57	M	W	2/ 6/36	1000	14	20	25.5	U	4	Yes	p.m.	20 hrs.
28.	1955	60	F	B	6/27/36	880	14	57	18.4	U	4	No	—	19 hrs.
29.	2035	65	F	B	10/ 1/36	520	13	60	24.9	U	4	Yes	p.m.	18 hrs.
30.	2081	52	F	B	12/ 5/36	720	13	55	39.5	U	—	Yes	p.m.	32 hrs.
31.	2089	52	M	W	12/15/36	1528	25	113	14.7	U	—	No	—	6 hrs.
32.	2100	59	F	W	12/26/36	1008	12	55	34.8	U	3	Yes	—	5 hrs.

ity is given. Because the 19 "C_3" cases recovered from the acidosis, the mortality has also been calculated with these cases regarded as recoveries instead of deaths, and "$R + C_3$" refers to total recoveries plus the "C_3" cases, and "$D - C_3$" refers to total deaths minus the "C_3" cases. If the 19 "C_3" cases are regarded as recoveries, the total mortality for the entire 268 cases becomes 36.6 per cent. In tables 5 and 6 the + and — signs in the "group" column indicate whether the CO_2 was above 40 prior to death.

In the 139 cases with complications there were 105 cases with infections, of which 68 occurred in the "B" group and 37 in the "C" group. The location of the infections was as follows: Respiratory system (except tu-

TABLE IV

PHILADELPHIA GENERAL HOSPITAL

Diabetic Acidosis with Complications. Cases Recovering (BR)

	Patient No.	Age	Sex	Color	Date Admitted	Blood Findings on Admission				On Admission			Group	Complications
						Sugar mg. %	CO_2 vol. %	Urea N mg. %	W.B.C. thous.	Mentally	Duration Acidosis	Known Diabetic		
1.	25	19	M	W	1/17/31	325	25	9	16.0	C	–	Yes	B2	Active pulmonary tuberculosis
2.	30	63	F	W	1/21/31	218	29	—	11.1	C	–	No	B2	Hyperthyroidism
3.	43	27	M	B	1/29/31	330	29	16	18.6	C	–	Yes	B1	Otitis media
4.	43	27	M	B	3/16/31	400	25	14	—	C	–	Yes	B2	Mastoiditis
5.	181	62	M	B	6/ 6/31	200	24	17	—	U	–	Yes	B2	Frontal lobe tumor—removed
6.	185	46	F	B	6/12/31	1056	18	55	27.7	U	4	No	B2	Broncho-pneumonia
7.	202	28	F	B	7/10/31	241	14	14	24.2	C	2	Yes	B2	Pulmonary abscess
8.	221	46	F	W	7/28/31	284	14	14	15.7	C	2	Yes	B2	Carbuncle of chin
9.	287	42	F	B	10/15/31	528	16	35	16.4	U	1	No	B2	Hyperthyroidism
10.	317	42	F	B	11/14/31	282	27	24	—	C	3	Yes	B1	Infectious arthritis
11.	252	16	M	B	12/18/31	574	17	14	26.4	C	3	Yes	B2	Broncho-pneumonia
12.	287	42	F	B	1/ 3/32	632	12	24	—	C	4	Yes	B2	Hyperthyroidism
13.	418	19	M	W	3/ 1/32	320	28	9	15.2	C	–	Yes	B2	Carbuncle of neck
14.	192	18	M	W	3/15/32	416	18	17	10.4	C	3	Yes	B2	Influenzal pneumonia
15.	443	39	M	W	3/20/32	662	12	22	31.5	C	4	Yes	B2	Erysipelas of face
16.	120	17	F	W	3/23/32	288	17	7	17.6	C	–	Yes	B1	Acute tonsillitis
17.	512	17	F	W	6/ 4/32	448	9	12	18.8	C	4	No	B2	Suppurative mastoiditis
18.	481	28	F	W	5/ 5/32	540	15	30	—	C	4	Yes	B2	Suppurative parotitis
19.	560	35	F	B	8/10/32	338	20	14	—	C	4	No	B1	Ischio-rectal abscess
20.	287	42	F	B	8/12/32	600	11	27	16.0	C	–	Yes	B2	Hyperthyroidism
21.	78	17	M	W	9/29/32	280	16	12	17.9	C	2	Yes	B1	Acute pharyngitis
22.	624	72	M	W	10/ 4/32	328	29	15	6.4	C	–	Yes	B2	Gangrene of foot
23.	721	57	M	W	1/12/33	262	27	27	—	C	–	Yes	B2	Erysipelas of face and back
24.	736	53	M	W	1/27/33	442	20	—	49.5	C	–	—	B2	Abscess of back
25.	178	16	F	W	4/21/33	428	29	12	15.8	C	1	Yes	B1	Suppurative endometritis
26.	884	40	F	B	6/ 6/33	406	17	22	18.4	C	–	No	B2	Carbuncle of back
27.	897	28	F	B	6/14/33	212	15	15	15.4	C	4	No	B1	Acute alcoholism
28.	919	57	F	W	7/10/33	224	29	11	—	C	4	No	B1	Infected foot
29.	319	15	F	W	9/30/33	380	18	15	21.4	C	1	Yes	B1	Acute enteritis
30.	936	55	M	W	10/15/33	178	27	27	13.2	C	1	Yes	B1	Acute alcoholism
31.	193	12	M	W	12/18/33	400	15	13	27.8	C	3	Yes	B1	Upper respiratory infection
32.	1072	33	M	W	1/ 7/34	536	11	20	23.2	C	3	Yes	B1	Acute enteritis
33.	453	16	M	W	9/ 6/34	520	24	47	4.5	C	3	Yes	B1	Ulcerative colitis
34.	1333	25	F	B	9/24/34	137	22	12	14.3	C	3	No	B2	Acute cholangitis
35.	1409	55	M	W	12/13/34	604	23	65	13.0	U	3	No	B2	Acute parotitis
36.	292	60	F	B	12/21/34	466	23	17	—	C	–	Yes	B2	Gangrene—thigh amputation
37.	1419	21	F	B	12/23/34	1850	13	95	12.7	C	3	No	B2	Lobar pneumonia
38.	1512	31	F	W	3/20/35	548	21	14	22.7	C	2	Yes	B1	Acute bronchitis
39.	1583	24	M	W	5/24/35	816	14	48	45.5	U	2	No	B1	Acute pharyngitis
40.	1128	17	F	W	5/29/35	232	29	15	—	C	–	Yes	B1	Upper respiratory infection
41.	1599	43	F	B	6/ 5/35	300	16	16	22.4	C	2	No	B2	Carbuncle of neck
42.	415	14	M	B	8/18/35	324	24	20	15.7	C	1	Yes	B1	Upper respiratory infection
43.	277	35	F	W	8/26/35	864	20	17	57.1	C	1	Yes	B1	Acute enteritis
44.	1583	24	M	W	9/25/35	428	25	17	16.6	C	3	Yes	B1	Acute alcoholism
45.	1757	58	F	B	11/12/35	345	20	16	14.6	C	3	Yes	B1	Fracture of ankle
46.	1772	44	M	B	11/22/35	310	29	18	12.8	C	3	Yes	B2	Prostatic abscess
47.	1474	13	F	W	12/18/35	300	23	16	12.8	C	1	Yes	B1	Upper respiratory infection
48.	1846	39	M	W	3/ 1/36	380	28	14	30.6	C	4	No	B1	Cellulitis of leg
49.	1614	45	M	W	4/29/36	1360	12	40	54.5	C	3	Yes	B1	Acute alcoholism
50.	1474	14	F	W	6/16/36	640	13	18	29.3	C	1	Yes	B2	Empyema
51.	1967	46	F	W	7/14/36	400	16	18	25.3	C	3	No	B2	Infected foot—thigh amputation
52.	1974	50	F	W	7/25/36	560	27	24	—	C	–	No	B2	Gangrene—thigh amputation
53.	2063	43	F	W	11/10/36	320	28	9	—	C	–	Yes	B2	Active pulmonary tuberculosis
54.	1450	18	F	B	11/26/36	420	6	16	30.0	C	3	Yes	B1	Abscess of thigh

berculosis) 36, gastrointestinal system 14, genito-urinary 9, skin and subcutaneous tissues 16, feet 16, miscellaneous 5, pulmonary tuberculosis 9. Of the 34 non-infections, 13 were in the "B" group and 21 in the "C" group. These consisted of coronary occlusion 7, hyperthyroidism 6, acute alcoholism 4, cancer 3, apoplexy 2, hypertensive congestive failure 2 and miscellaneous 10.

Of the 117 cases which died, postmortem examinations were made in 68 cases, 58.1 per cent of the deaths. Postmortem examinations are indispensable for making accurate final diagnoses in cases dying in diabetic acidosis. When patients in acidosis are admitted with inadequate histories or no histories at all, and die without coming out of acidosis, the presence of complications, their nature and severity often can only be guessed at, and not infrequently they are missed entirely unless postmortem examinations are made. Recent examples of cases in which the complication was not diagnosed during life are patients 1985 (C 36), 1999 (C 37) and 2076 (C 39). The first case was a colored woman aged 49, admitted 8/5/36. She was not known to be diabetic. Her sister stated that she had been working until three days prior to admission and for three days had been extremely weak. She was unconscious at admission and died in 31 hours. At autopsy miliary tuberculosis was found. The second case was a colored woman aged 76, admitted 8/27/36. A friend stated she had been well until seven days prior to admission, since when she had been weak and compelled to stay in bed. Her friend knew she was a large water drinker but did not know whether she had diabetes. Her urine contained large numbers of leukocytes. She was unconscious at admission and died in 17 hours. At autopsy multiple abscesses of the kidneys were found. The third case was

TABLE V

PHILADELPHIA GENERAL HOSPITAL

Diabetic Acidosis with Complications. Cases Dying (BD)

	Patient No.	Age	Sex	Color	Date Admitted	Blood Findings on Admission				On Admission			Group	Complications	Post mortem	Time Lived
						Sugar mg. %	CO_2 vol. %	Urea N mg. %	W.B.C. thous.	Mentally	Duration Acidosis	Known Diabetic				
1.	309	64	M	W	11/ 9/31	298	24	110	4.0	C	4	No	B2+	Empyema of gall-bladder	—	24 hrs.
2.	399	4	M	W	2/ 7/32	440	14	—	43.5	C	-	Yes	B1−	Pertussis	p.m.	7 hrs.
3.	452	47	F	B	4/12/32	900	23	48	18.3	U	3	No	B2+	Lobar pneumonia	—	26 hrs.
4.	561	55	F	W	8/12/32	400	10	28	—	U	3	Yes	B2−	Erysipelas	—	18 hrs.
5.	603	38	F	B	9/20/32	460	15	16	—	U	2	Yes	B1+	Abscess of Bartholin's gland	p.m.	12 hrs.
6.	631	39	M	B	10/13/32	500	27	53	—	C	4	No	B2+	Portal cirrhosis; pneumonia	p.m.	12 hrs.
7.	636	62	F	B	10/19/32	300	9	25	—	U	4	Yes	B2−	Septicemia	—	11 hrs.
8.	287	43	F	B	12/ 6/32	640	16	55	73.2	U	—	Yes	B2+	Hyperthyroidism	p.m.	22 hrs.
9.	750	61	F	W	2/10/33	486	24	26	—	U	2	No	B2−	Resolving pneumonia	—	2 hrs.
10.	906	66	F	W	6/24/33	440	19	30	—	C	-	No	B2−	Acute pleurisy	—	9 hrs.
11.	1067	57	F	W	1/ 2/34	380	13	23	18.6	U	4	Yes	B2−	Coronary occlusion	p.m.	11 hrs.
12.	360	22	M	W	2/21/34	464	14	—	—	U	3	Yes	B2+	Abscess of jaw	—	5 hrs.
13.	1164	62	F	W	4/ 8/34	456	24	49	—	C	1	Yes	B2−	Active pulmonary tuberculosis	p.m.	12 hrs.
14.	1196	48	F	B	5/ 9/34	480	21	40	—	U	-	No	B2+	Tuberculous pneumonia	—	10 hrs.
15.	1198	56	F	W	5/10/34	620	15	97	—	C	2	Yes	B2+	Gangrene of foot	—	14 hrs.
16.	1211	42	F	W	5/24/34	402	16	36	—	U	3	Yes	B2−	Erysipelas of face	—	8 hrs.
17.	1268	33	F	B	7/ 7/34	370	22	21	14.2	C	4	No	B2+	Pelvic inflammatory disease	—	18 hrs.
18.	1272	34	F	B	7/21/34	736	18	—	—	U	4	No	B2−	Gas gangrene of buttocks	—	9 hrs.
19.	1342	54	F	B	10/ 5/34	1008	22	95	25.8	U	3	No	B2+	Gangrene—thigh amputation	p.m.	59 hrs.
20.	1402	61	F	W	12/ 4/34	370	19	15	15.9	C	4	Yes	B2+	Broncho-pneumonia	p.m.	49 hrs.
21.	1415	56	F	W	12/18/34	412	15	26	16.5	C	4	No	B2−	Broncho-pneumonia	—	12 hrs.
22.	1483	56	F	W	2/28/35	1470	10	42	25.0	U	3	Yes	B2−	Gangrene of both feet	p.m.	2 hrs.
23.	1760	48	F	B	11/13/35	540	10	56	14.1	U	4	No	B1+	Bilateral parotitis	p.m.	5 days
24.	1840	48	F	B	2/20/36	1290	16	60	24.0	U	4	No	B2+	Gangrenous cecum peritonitis	p.m.	39 hrs.
25.	1376	65	F	W	7/11/36	400	13	26	—	U	4	Yes	B2−	Fractured ribs hemothorax	p.m.	1 hr.
26.	1545	65	F	W	9/19/36	440	24	52	12.8	C	4	Yes	B2−	Pyelonephritis	—	18 hrs.
27.	2073	51	F	W	11/21/36	240	27	11	16.6	C	4	Yes	B2+	Carbuncle of neck; pneumonia	p.m.	3 days

TABLE VI

PHILADELPHIA GENERAL HOSPITAL

Diabetic Acidosis. Cases Dying from Complications (C)

	Patient No.	Age	Sex	Color	Date Admitted	Blood Findings on Admission				On Admission			Group	Complications	Post mortem	Time Lived
						Sugar mg.%	CO_2 vol. %	Urea N mg. %	W.B.C. thous.	Mentally	Duration Acidosis	Known Diabetic				
1.	34	14	F	W	3/ 8/31	278	14	14	24.5	C	4	Yes	C1+	Influenza	p.m.	4 days
2.	253	60	M	W	8/25/31	202	28	28	33.6	C	–	—	C2–	Coronary occlusion	—	17 hrs.
3.	279	19	F	W	10/ 1/31	656	18	22	25.8	U	3	No	C1+	Ruptured appendix peritonitis	—	4 days
4.	295	63	F	W	10/24/31	456	29	45	15.0	U	4	Yes	C2+	Coronary occlusion	—	24 hrs.
5.	306	45	M	W	11/ 5/31	290	22	10	—	C	4	No	C2+	Lobar pneumonia	—	7 days
6.	349	60	F	W	12/27/31	512	14	40	—	C	4	Yes	C1+	Lobar pneumonia with abscess	p.m.	20 hrs.
7.	586	55	M	W	9/ 8/32	480	11	21	24.9	C	1	Yes	C2–	Gangrene of foot	p.m.	7 hrs.
8.	611	49	F	W	9/24/32	532	17	16	19.9	U	3	Yes	C2–	Active pulmonary tuberculosis	—	13 hrs.
9.	639	54	M	W	10/21/32	372	26	14	36.6	C	–	Yes	C2+	Septicemia staphylococcus aureus	p.m.	48 hrs.
10.	655	57	M	W	11/ 9/32	414	27	26	35.4	C	3	No	C2+	Carbuncle of neck	—	14 hrs.
11.	714	42	F	W	1/ 8/33	468	18	10	—	C	–	No	C1+	Lobar pneumonia	—	6 days
12.	715	50	F	W	1/ 9/33	536	25	14	14.5	C	2	Yes	C2+	Cerebral thrombosis	—	24 hrs.
13.	732	46	F	B	1/24/33	486	15	63	7.5	U	3	No	C2–	Acute hemorrhagic pancreatitis	p.m.	16 hrs.
14.	759	74	F	W	2/16/33	588	17	—	17.6	U	3	Yes	C2–	Gangrene of foot; abscess of back	p.m.	12 hrs.
15.	765	50	F	B	2/22/33	640	13	50	15.5	U	2	No	C2–	Acute hemorrhagic pancreatitis	p.m.	22 hrs.
16.	768	52	F	W	2/26/33	486	28	22	—	U	1	—	C2+	Cerebral thrombosis	p.m.	15 hrs.
17.	205	74	M	W	8/10/33	96	26	20	—	U	2	Yes	C2–	Abdominal carcinomatosis	p.m.	8 hrs.
18.	1021	65	F	W	10/ 8/33	202	13	—	4.0	U	4	—	C2–	Pernicious anemia (?)	—	7 hrs.
19.	427	27	F	W	1/ 1/34	636	22	28	—	C	–	Yes	C2–	Carbuncle of chin; abscess of kidney	—	27 hrs.
20.	785	58	F	W	1/20/34	496	23	38	45.3	C	4	Yes	C1+	Broncho-pneumonia	—	3 days
21.	1092	43	F	B	1/26/34	592	19	15	24.3	U	4	No	C2+	Coronary occlusion	p.m.	2 days
22.	1143	29	F	B	3/20/34	504	18	12	13.0	C	3	Yes	C2–	Peritonitis	—	17 hrs.
23.	1146	46	F	B	3/22/34	508	13	16	14.5	C	–	No	C2+	Tuberculous pneumonia	p.m.	18 hrs.
24.	1151	40	F	B	3/24/34	608	15	29	22.3	U	4	No	C2+	Gangrene of both feet	p.m.	16 hrs.
25.	1183	60	F	W	4/27/34	640	14	—	23.1	C	1	No	C2–	Carcinoma of cervix	—	12 hrs.
26.	1411	73	F	W	12/14/34	400	15	16	9.5	C	2	No	C2+	Broncho-pneumonia; septicemia	—	16 hrs.
27.	1467	55	F	W	2/12/35	280	23	125	50.9	C	3	Yes	C2–	Coronary occlusion	—	16 hrs.
28.	1592	72	F	W	5/30/35	320	24	17	28.0	C	–	Yes	C2+	Gangrene—thigh amputation	p.m.	57 hrs.
29.	1595	48	F	W	6/ 1/35	704	26	52	11.9	U	–	No	C2–	Chronic pancreatitis with stone	p.m.	7 hrs.
30.	616	60	M	W	7/25/35	280	12	165	26.1	U	–	Yes	C2–	Pyelonephritis; prostatic abscess	p.m.	4 hrs.
31.	1649	83	F	W	8/ 4/35	896	18	53	14.5	U	2	Yes	C2+	Abscesses of kidneys and lungs	p.m.	11 hrs.
32.	1707	44	F	W	9/29/35	290	10	15	40.9	U	4	Yes	C2+	Gangrenous ileum; peritonitis	p.m.	34 hrs.
33.	1732	40	F	B	10/20/35	568	22	40	—	U	–	No	C2–	Gas gangrene of arm	p.m.	2 hrs.
34.	1783	62	F	W	12/ 3/35	456	21	29	21.0	C	3	Yes	C2+	Carcinoma of both breasts	p.m.	20 hrs.
35.	1838	40	F	B	2/17/36	800	12	60	16.4	U	4	No	C1+	Broncho-pneumonia	p.m.	8 days
36.	1985	49	F	B	8/ 5/36	874	10	46	12.1	U	3	No	C2+	Miliary tuberculosis	p.m.	31 hrs.
37.	1999	76	F	B	8/27/36	680	12	60	29.7	U	4	—	C2+	Abscesses of kidneys	p.m.	17 hrs.
38.	1270	64	F	W	9/16/36	490	29	38	—	C	–	Yes	C2–	Coronary occlusion	p.m.	1½ hrs.
39.	2076	55	F	W	11/26/36	310	14	21	19.5	C	4	No	C2–	Ruptured appendix; peritonitis	p.m.	1½ hrs.
40.	160	60	F	B	5/15/31	976	24	63	16.8	C	2	No	C3+	Gangrene of foot	p.m.	10 days
41.	248	20	F	W	8/21/31	268	29	11	—	C	3	Yes	C3+	Active pulmonary tuberculosis	—	35 days
42.	286	40	F	B	10/24/31	488	26	65	—	C	–	No	C3+	Chronic nephritis	p.m.	9 days
43.	459	45	F	B	4/18/32	480	26	90	29.9	C	–	Yes	C3+	Subacute nephritis	p.m.	8 days
44.	704	52	F	B	1/ 6/33	640	18	52	7.8	C	1	No	C3+	Abscesses of kidneys	p.m.	6 days
45.	872	73	F	B	5/24/33	350	29	25	18.4	C	4	Yes	C3+	Bilateral suppurative pyelonephritis	p.m.	13 days
46.	924	52	F	W	7/13/33	332	15	11	18.0	C	–	Yes	C3+	Gangrene—thigh amputation	p.m.	5 days
47.	1033	44	F	W	11/ 6/33	355	22	15	—	C	3	Yes	C3+	Mastoiditis with multiple abscesses	—	61 days
48.	1076	37	M	W	1/10/34	372	25	11	—	C	–	Yes	C3+	Pulmonary abscess	—	15 days
49.	1255	26	M	W	6/29/34	308	27	14	—	C	–	No	C3+	Dysinsulinism	p.m.	67 days
50.	588	26	F	W	10/22/34	260	28	8	—	C	–	Yes	C3+	Active pulmonary tuberculosis	p.m.	82 days
51.	1304	56	F	B	11/ 2/34	420	27	39	14.1	U	1	Yes	C3+	Hypertensive cardio-vascular disease	—	12 days
52.	1418	56	F	B	12/22/34	480	23	50	16.0	C	4	Yes	C3+	Hypertensive cardio-vascular disease	p.m	42 days
53.	1456	61	F	B	2/ 1/35	736	18	30	23.4	U	1	No	C3+	Dermatitis gangrenosa	p.m.	54 days
54.	1473	67	M	W	2/19/35	388	21	16	25.9	C	—	Yes	C3+	Coronary occlusion	p.m.	16 days
55.	1477	38	F	W	2/24/35	926	23	88	12.7	C	3	No	C3+	Pyelonephritis	p.m.	22 days
56.	1515	59	F	B	3/25/35	572	29	50	23.1	C	3	Yes	C3+	Hyperthyroidism	—	9 days
57.	1095	39	F	W	1/12/36	688	12	22	24.8	C	1	Yes	C3+	Mastoiditis; cellulitis of face	p.m.	39 days
58.	1899	58	F	B	4/25/36	488	13	7	46.3	C	–	Yes	C3+	Carbuncle of thigh; pulmonary embolism	p.m.	12 days

a white woman, aged 55, admitted 11/26/36. She was rational and neither she nor her husband knew that she had diabetes. She was well until November 20 when she ate some pie which caused severe abdominal pain. On November 21 and 22 she vomited and had marked obstipation, and the next day pains in the chest. A doctor was not called until November 26. At

TABLE VII

PHILADELPHIA GENERAL HOSPITAL

Recoveries and Deaths from Diabetic Acidosis with Reference to Blood Sugar at Admission

	Below 201	201 300	301 400	401 500	501 600	601 700	701 800	801 900	901 1000	Above 1000	Average B. S.
AR	1	14	34	16	7	8	7	3	3	4	487
AD	1	0	3	5	4	1	8	2	4	4	713
BR	3	12	14	8	8	4	0	2	0	3	461
BD	0	3	5	11	1	2	1	1	0	3	554
C_1C_2	1	7	4	9	8	6	2	2	0	0	488
C_3	0	2	6	5	1	2	1	0	2	0	501
R	4	26	48	24	15	12	7	5	3	7	478
D	2	12	18	30	14	11	12	5	6	7	567
	R 78 D 32	29.1%		R 51 D 55	51.9%		R 22 D 30	57.7%			
$R+C_3$	4	28	54	29	16	14	8	5	5	7	480
$D-C_3$	2	10	12	25	13	9	11	5	4	7	580
	R 86 D 24	21.8%		R 59 D 47	44.4%		R 25 D 27	52.0%			

TABLE VIII

PHILADELPHIA GENERAL HOSPITAL

Cases of Diabetic Comá in Which the Blood Sugar Was 1000 mg. % or Above

	Name	Age	Sex	Color	Date Admitted	No. of Admission	Blood Findings on Admission			Outcome	Post Mortem
							Sugar mg. %	CO_2 vol. %	Urea N mg. %		
1.	T. J.	40	M	B	11/23/25	1	1520	21	—	Died 3 hrs.	p.m.
2.	M. M.	58	F	W	4/ 2/26	1	1120	—	45	Recovered	
3.	T. M.	27	M	W	1/12/27	5	1484	11	—	Died 8 hrs.	—
4.	E. T.	50	F	B	7/19/28	1	1060	8	30	Died 16 hrs.	p.m.
5.	H. H.	30	F	B	3/30/29	1	1080	11	21	Recovered	
6.	G. M.	28	F	B	12/11/29	1	1030	12	50	Died 25 hrs.	p.m.
7.	J. J.	35	M	B	1/29/30	1	1500	24	—	Died 8 hrs.	p.m.
8.	H. H.	31	F	B	5/14/30	2	1056	10	—	Died 6 hrs.	p.m.
9.	C. R.	46	F	B	6/12/31	1	1056	18	55	Recovered	
10.	S. D.	20	F	W	9/11/31	17	1000	16	—	Died at adm.	—
11.	L. J.	53	F	B	6/10/34	1	1028	12	—	Died 2 hrs.	p.m.
12.	M. H.	54	F	B	10/ 5/34	1	1008	22	95	Died 59 hrs.	p.m.
13.	M. S.	40	F	W	10/ 9/34	6	1000	7	20	Died 16 hrs.	—
14.	N. D.	21	F	B	12/23/34	1	1850	13	95	Recovered	
15.	F. C.	39	F	B	1/20/35	1	1024	15	63	Recovered	
16.	S. P.	56	F	W	2/28/35	1	1470	10	42	Died 2 hrs.	p.m.
17.	J. P.	22	M	B	3/20/35	1	1056	14	43	Recovered	
18.	G. H.	36	M	B	5/16/35	1	1256	18	78	Died 2 hrs.	p.m.
19.	M. F.	59	F	W	1/12/36	4	1080	15	75	Recovered	
20.	J. T.	57	M	W	2/ 6/36	3	1000	14	20	Died 20 hrs.	p.m.
21.	H. M.	48	F	B	2/20/36	1	1290	16	60	Died 39 hrs.	p.m.
22.	M. G.	45	M	W	4/29/36	2	1360	12	40	Recovered	
23.	M. G.	45	M	W	8/ 8/36	3	1168	17	55	Recovered	
24.	A. H.	52	M	W	12/15/36	1	1528	25	113	Died 6 hrs.	p.m.
25.	E. G.	59	F	W	12/26/36	1	1008	12	55	Died 5 hrs.	—

admission it was noted that she had slight abdominal distention, no tenderness, no masses and no peristalsis. She died suddenly one and one-half hours after admission. At autopsy it was discovered that she had a ruptured appendix and peritonitis.

TABLE IX

PHILADELPHIA GENERAL HOSPITAL

Recoveries and Deaths from Diabetic Acidosis with Reference to CO_2 at Admission

	Below 11	11–15	16–20	21–25	26–29	Average CO_2
AR	2	30	28	29	8	18.7
AD	2	19	4	4	3	16.0
BR	2	13	14	11	14	20.2
BD	4	7	6	8	2	18.0
C_1C_2	2	14	7	8	8	18.8
C_3	0	3	2	6	8	22.8
R	4	43	42	40	22	19.2
D	8	43	19	26	21	18.5
$R+C_3$	4	46	44	46	30	19.6
$D-C_3$	8	40	17	20	13	17.6
	66.7%	46.5%	27.9%	30.3%	30.2%	

TABLE X

PHILADELPHIA GENERAL HOSPITAL

Recoveries and Deaths from Diabetic Acidosis with Reference to Blood Urea Nitrogen at Admission

	Below 21	21–40	41–60	Above 60	Not Done	Average B. U. N.
AR	66	23	4	4	0	20.5
AD	6	8	8	6	4	44.7
BR	36	11	3	2	2	21.6
BD	3	10	8	3	3	43.3
C_1C_2	13	13	7	3	3	35.8
C_3	7	5	3	4	0	36.7
R	102	34	7	6	2	20.9
D	29	36	26	16	10	40.0
	22.1%	51.4%	78.8%	72.7%		
$R+C_3$	109	39	10	10	2	23.8
$D-C_3$	22	31	23	12	10	42.1
	16.8%	44.3%	69.7%	54.5%		

Among the 29 cases in the "BD" and "C_1C_2" groups in which postmortem examinations were not made, it is quite likely that we have made some mistakes in diagnosing complications which did not exist. It is also just as likely that we missed complications in the "AD" group in the 15 cases in which there was no autopsy.

In the total number of cases there were many of unusual interest, two of which we feel deserve short descriptions. Patient 1594 (AD 25) is included in the AD group, although he died 21 days after admission. At postmortem examination no cause for his death could be found other than

TABLE XI

PHILADELPHIA GENERAL HOSPITAL

Recoveries and Deaths from Diabetic Acidosis with Reference to Leukocytosis at Admission

	— 10.0	10.1 20.0	20.1 30.0	30.1 40.0	40.1 50.0	50.1 +	Not Done	Average W.B.C.
AR	6	28	23	2	5	3	30	22.2
AD	3	9	8	3	1	0	8	20.4
BR	2	23	11	2	2	2	12	21.6
BD	1	8	3	0	1	1	13	23.0
C_1C_2	3	12	10	3	2	1	8	22.5
C_3	1	6	5	0	1	0	6	21.3
R	8	51	34	4	7	5	42	22.0
D	8	35	26	6	5	2	35	21.8
$R+C_3$	9	57	39	4	8	5	48	21.9
$D-C_3$	7	29	21	6	4	2	29	21.9

TABLE XII

PHILADELPHIA GENERAL HOSPITAL

Recoveries and Deaths from Diabetic Acidosis with Reference to Age

	Below 11	11 20	21 30	31 40	41 50	51 60	61 70	Above 70	Average Age
AR	4	40	23	9	11	9	0	1	27.1
AD	0	3	6	6	4	11	2	0	41.8
BR	0	16	9	7	12	7	2	1	34.5
BD	1	0	1	4	6	7	8	0	49.4
C_1C_2	0	2	2	3	11	11	4	6	52.6
C_3	0	1	2	4	2	7	2	1	47.8
R	4	56	32	16	23	16	2	2	29.7
D	1	6	11	17	23	36	16	7	48.2
	R 92 D 18	16.4%		R 39 D 40	50.6%	R 20 D 59	74.7%		
$R+C_3$	4	57	34	20	25	23	4	3	31.8
$D-C_3$	1	5	9	13	21	29	14	6	48.2
	R 95 D 15	13.6%		R 45 D 34	43.0%	R 30 D 49	62.0%		

lesions in his brain which we have described [5] in other cases dying from diabetic acidosis. Patient 1255 (C 49) is diagnosed "dysinsulinism." His history strongly suggested spells of spontaneous hypoglycemia at times for a period of two years. He was admitted in diabetic acidosis and took moderate doses of insulin for three weeks. He then began to have very severe

spontaneous hypoglycemia which could not be controlled. Two months after admission a laparotomy was done in the hope of finding a pancreatic adenoma. None was found and part of the pancreas was resected, from which he died two days later.

In estimating at the time of admission the prognosis of a case of acidosis,

TABLE XIII

PHILADELPHIA GENERAL HOSPITAL

Recoveries and Deaths from Diabetic Acidosis with Reference to Sex and Color

	Male	Female	White	Black
AR	34	64	57	40
AD	10	22	22	10
BR	23	31	33	21
BD	4	23	16	11
C_1C_2	7	32	29	10
C_3	3	16	9	10
R	57	94	90	61
D	24	93	76	41
	29.6%	49.7%	45.8%	40.2%
$R+C_3$	60	110	99	71
$D-C_3$	21	77	67	31
	25.9%	41.2%	40.4%	30.4%

TABLE XIV

PHILADELPHIA GENERAL HOSPITAL

Recoveries and Deaths from Diabetic Acidosis with Reference to Mental State at Admission

	Conscious	Unconscious
AR	87	10
AD	5	27
BR	49	5
BD	11	16
C_1C_2	20	19
C_3	17	2
R	136	15
D	53	64
	28.0%	81.0%
$R+C_3$	153	17
$D-C_3$	36	62
	19.0%	78.5%

first of all we should like to know what complication may be present and its severity. Of the 139 cases with complications, 85 died, a mortality of 61.2 per cent. As we have already pointed out, it often happens that no judgment can be formed as to the part a complication is playing until after the patient has been under treatment a considerable period of time, and the very presence of a complication may not be suspected until the postmortem ex-

amination. It is only in cases in which the complication is fairly evident at the time of admission that the question of a complication can be given much consideration in estimating the prognosis. Our procedure in this report has been to group the cases according to the outcome of the cases, and then to examine the data which were known within the first hour after admission in order to estimate what inference regarding prognosis may be drawn from each datum.

Blood Sugar (table 7). The degree of hyperglycemia is not usually considered to have much effect on mortality. Certainly no one believes that diabetics die from high blood sugar. But when the blood sugar is very high the factors which do cause death are more likely to be present. The mortality for all the cases in which the blood sugar was above 700 was

TABLE XV

PHILADELPHIA GENERAL HOSPITAL

Recoveries and Deaths from Diabetic Acidosis with Reference to Hours in Acidosis at Admission

	Below 13	13–24	25–48	Above 48	Not Known	% Cases above 24 hrs.
AR	14	18	21	19	25	55.5%
AD	3	4	10	11	4	75.0%
BR	8	6	15	9	16	63.2%
BD	1	3	6	13	4	82.6%
C_1C_2	3	5	9	12	10	72.4%
C_3	4	1	4	2	8	54.5%
R	22	24	36	28	41	58.2%
D	11	13	29	38	26	73.6%
	33.3%	35.1%	44.6%	57.6%		
$R+C_3$	26	25	40	30	49	
$D-C_3$	7	12	25	36	18	
	21.2%	32.4%	38.5%	54.5%		

57.7 per cent, whereas for the cases for which it was 400 or lower, it was 29.1 per cent. If the "C_3" cases be regarded as recoveries, the mortality was 52.0 per cent and 21.8 per cent respectively, about two and one-half times as high in the high blood sugar group as in the low one. Among the uncomplicated cases it may be pointed out that the average blood sugar in the "AR" group was 487, and in the "AD" group 713. When the blood sugar is very high, therefore, we are justified in anticipating a higher mortality than when it is low.

We have previously published [4] 16 cases in which the blood sugar was 1000 or above, the first case occurring in 1925. We now add nine additional ones (table 8). Of the total of these cases nine recovered and 16 died. Case 10 does not appear in tables 2 to 6 as she arrived in the receiving ward moribund and died a few minutes after her blood had been taken and sent to the metabolic laboratory. Case 14 had a blood sugar of 1850,

the highest in the literature in which recovery occurred. Cases 22 and 23 are the same individual, a white man aged 45.

CO_2 Volume Per Cent (table 9). The degree of chemical acidosis is measured by the CO_2 combining power measured in volumes per cent. As might be anticipated, the mortality is higher the lower the CO_2. This becomes clear, however, chiefly in the uncomplicated cases. The presence in the total series of a large number of cases with severe complications masks the effect of the acidosis.

In determining a criterion of acidosis according to which the selection of cases for this report might be made the level of 29 volumes per cent CO_2 was selected for the following reasons. The unusual figure 29, instead of some multiple of five or ten, comes about by virtue of the fact that many years ago our laboratory began to keep its CO_2 files in groups of 10, 60 to 69, 50 to 59, etc. We feel justified in including the group 20–29, because in this group out of 109 cases there were 47 deaths, in seven of which no other cause of death was found.

At the low extreme our chemists have reported no value lower than six. The analyses are made routinely within 20 minutes after the blood is withdrawn. When the observed volume of gas is very low, in addition to technical difficulties is the fact that the corrections become larger than the final result, and therefore of relatively great importance. The chief difficulty, however, is that when the CO_2 combining power is as low as 2 volumes per cent, as reported by several observers, the corresponding alveolar CO_2 tension, at a pH compatible with life, should require a ventilation rate of approximately 40 liters per minute in order to rid the body of the CO_2 of metabolism. This is a matter for the chemists to settle, and from the clinical point of view is only of academic interest.

Blood Urea Nitrogen (table 10). The effect of an abnormal blood urea nitrogen is more striking than either an increase in blood sugar or a decrease in CO_2. As the blood urea nitrogen increases above 20 mg. per cent the mortality increases rapidly. In the total series the mortality for cases with 20 mg. and below was 22.1 per cent, whereas for those cases with more than 20 mg. the mortality was 62.4 per cent. This increase in mortality is also clearly seen in the uncomplicated cases, being 8.3 per cent for the cases of 20 mg. and below, and 41.5 per cent for the cases of 21 mg. and above. The average blood urea nitrogen in the " AR " cases was 20.5 mg. per cent and the average in the " AD " cases 44.7 mg. per cent.

Leukocytosis (table 11). In 77 cases the white blood count is not included in this report, either because it was not done or because it was not done until some hours had elapsed after treatment was begun. The white count usually drops rapidly as treatment progresses. In the 191 cases in which a white count was made at admission it is noteworthy that it was above 10,000 in all but 16 cases. There is no correlation between the degree of leukocytosis and the mortality. More important is the fact that the

degrees of leukocytosis seem to be about the same for the uncomplicated cases and for those in which complications are present. Even when the leukocytosis is marked, it does not add to the evidence in favor of a complication. There were 19 cases with white counts above 40,000 of which nine were uncomplicated and 10 had complications, which is almost exactly the ratio of complicated-uncomplicated cases in the entire report (129 to 139). The two highest counts were on patients 1827 (AR 83) 72,100 and patient 287 (BD 8) 73,200.

Age (table 12). The increase in mortality with advancing years is very striking. This increase is due in part to the larger amount of death-dealing complications which begin to appear at about age 40, and in part to the inability of older patients to withstand the acidosis itself. The total mortality for patients up to 30 years was 16.4 per cent while for those over 50 years it was 74.7 per cent; with the " C_3 " cases regarded as recoveries, 13.6 per cent and 62.0 per cent respectively. Of the " A " cases 30 years of age and under, 67 recovered and nine died; of these nine, seven were unconscious when admitted and six had been in acidosis over 24 hours. On the other hand, of the cases over 50 years of age 10 recovered and 13 died. The average age for the " AR " group was 27.1 years and for the " AD " group 41.8 years. The average of all 268 cases was 37.8 years.

Sex and Color (table 13). There are 81 males and 187 females in this series, the total mortality being 29.6 per cent for the males and 49.7 per cent for the females. In the uncomplicated cases the mortality is only a little larger for the females. In the " BD," " C_1C_2 " and " C_3 " groups, however, there are 71 females and only 14 males. This disproportionately larger number of females is hard to account for. It is not due to diseases of the female organs. It is our impression that the presence of this great number of serious complications in women is due to greater negligence and less willingness to go to a hospital until driven to it. Our experience with our entire clinic, however, is that once in the hospital the women are more anxious to stay on than the men.

The population of Philadelphia is 11.3 per cent colored and the patients admitted to the metabolic division are approximately 20 per cent colored. In this report there are 166 white cases in 144 patients and 102 colored cases in 80 patients. The incidence of acidosis is, therefore, about two and one-half times as great in our colored patients. The mortality, however, is somewhat lower in the colored, but this is mostly accounted for by the greater percentage of return cases. Of the 44 return cases, 22 are white and 22 colored; two white cases died and one colored.

Mental State (table 14). The cases have been divided into conscious and unconscious groups, according as to whether it was possible to arouse them sufficiently to answer " Yes " or " No " to some simple question. The importance of the mental state in the prognosis is very great. The total mortality for the conscious patients was 28.0 per cent and for the uncon-

scious patients 81.0 per cent; with the "C_3" cases regarded as recoveries 19.0 per cent and 78.5 per cent. In other words a conscious patient is about four times as likely to recover from the acidosis as an unconscious one. In the uncomplicated cases, only 5.4 per cent of the conscious cases died whereas 73.0 per cent of the unconscious cases died.

Hours in Acidosis (table 15). We have been able to tabulate the cases according to the duration of the acidosis only in general terms. Even if an accurate history is available, when, from the history alone, may a patient be said to begin to be in acidosis? We have taken as our criterion the onset of nausea and vomiting, or when this symptom was not mentioned in the history or not present, we have taken the statement that the patient definitely became drowsy. In 67 cases it was impossible to make any estimation. According to the duration of the acidosis the cases have been divided into four groups: (1) Up to 12 hours, (2) 13 to 24 hours, (3) 25 to 48 hours, and (4) 49 hours and above. As might be expected the mortality increases rapidly with the duration of the acidosis as shown in table 15.

There are, of course, other important clinical data which aid in estimating the prognosis, chief of which is the state of the cardio-vascular system. When the blood pressure is very low at admission or falls during the course of treatment, this is of very evil omen. We have not been able to present this in the form of a table. Of great importance, also is the rapidity with which a patient responds to treatment. We are confining ourselves in this report, however, to the data which are available during the first hour after admission.

It is obvious from the above data that a much more accurate prognosis can be given from the clinical data than from the laboratory data. In estimating the prognosis of a given patient or in comparing the mortality of one series of comas as compared with some other series, it is far more important to know the complications present, the mental state, the age of the patients, and the duration of the acidosis, than it is to know the blood sugar, the CO_2 and the urea nitrogen. As regards treatment, however, frequent estimations of the blood sugar and CO_2 during the course of the acidosis are indispensable in properly gauging the doses of insulin and glucose.

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HYPERTHYROIDISM IN THE NEGRO *

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A REVIEW of current literature and monographs which deal with diseases of the thyroid gland gives definitely the impression that hyperthyroidism is uncommon in the negro.[1, 2] We have been impressed with the fallacy of this current belief. From the files of the St. Philip Hospital † for negroes we have selected records of 37 patients admitted during the past five years which justify an unequivocal diagnosis of Graves' disease.

Twenty-seven of the patients lived in the city of Richmond and the remaining 10 in the adjoining counties; this entire section of Virginia is geographically a tidewater area and is distinctly a non-endemic goiter zone.

Throughout the period of this study we have been impressed with the fact that hyperthyroidism in the negro is invariably definite and characteristic in its clinical manifestations. The symptoms begin abruptly, invariably pursue a progressive course with increasing intensity, spontaneous remissions rarely if ever occur, and iodine induced remissions are of brief duration.

Regardless of age, the clinical behavior of the patients and the observed physical phenomena were characteristically typical of the Graves' syndrome (figure 1). In only one patient was there made the diagnosis of thyroid adenomata with hyperthyroidism. In the remaining 36 patients the clinical picture was that of exophthalmic goiter. That this clinical impression was correct is substantiated by the histologic changes observed in the glands removed surgically. Thirty-three of the 34 specimens showed varying degrees of diffuse hyperplasia.

In addition to the usual symptoms and signs observed in Graves' disease, others of peculiar interest are frequently present in negro patients. The most characteristic and constant phenomena occurring in the finger nails are illustrated in figure 2. The nails are brittle and thin, but stiff; and, when the examining finger is drawn across the edge, it causes the sensation as of scraping the sharp edge of a razor blade. The nails become undermined and there is a definite line of pigmentation at the point of fusion of the excavated and non-excavated portion.

We have followed many of the patients after the basal metabolism was reduced to normal by a subtotal thyroidectomy and observed a disappearance of the abnormality of the nails with an improvement of general nutrition.‡

* Read at the St. Louis meeting of the American College of Physicians, April 21, 1937.
From the Hospital Division, Medical College of Virginia, Richmond, Virginia.

† St. Philip Hospital, a part of the Hospital Division of the Medical College of Virginia, is for negro patients only.

‡ These changes occur also in the white race, but are neither so constant nor so evident.

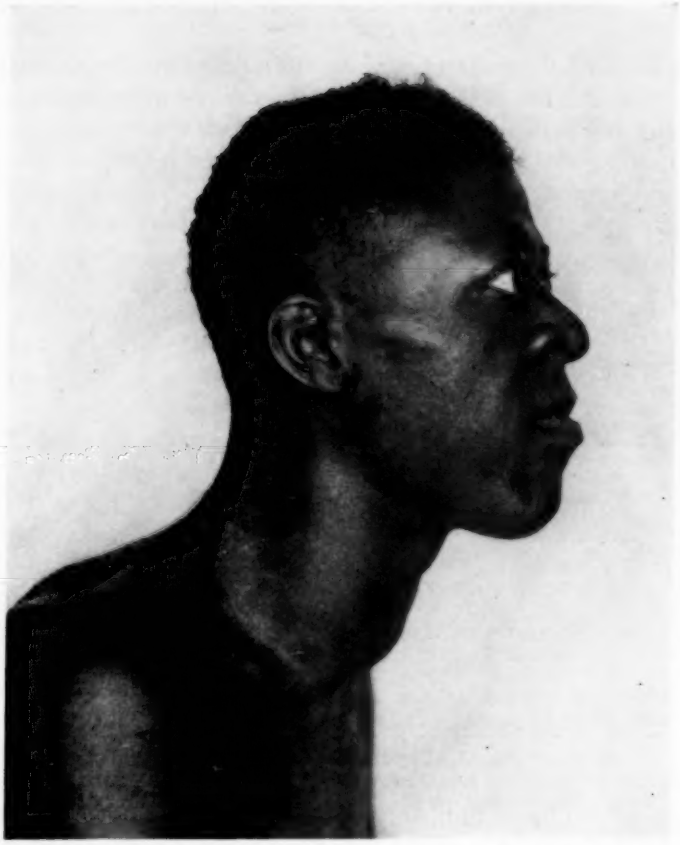

FIG. 1. Illustrating our conception of Graves' disease in a negro.

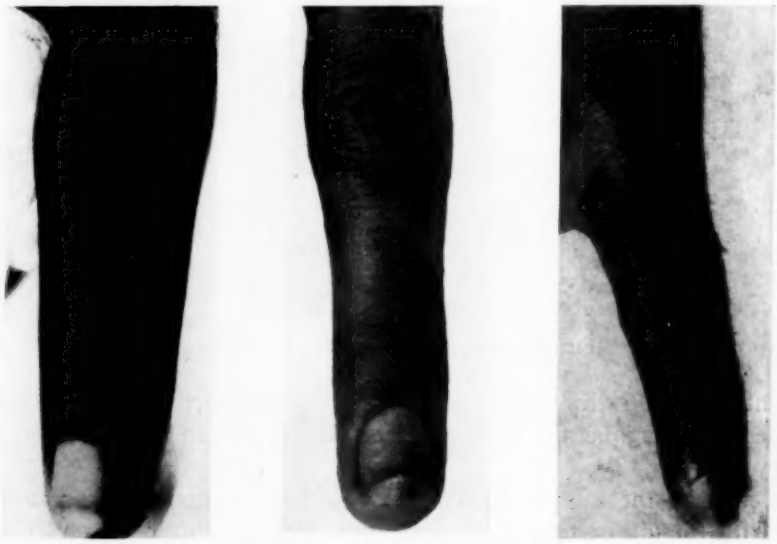

FIG. 2. The nail changes in exophthalmic goiter. Note that manicuring has not altered the basic characteristics.

Pigmentation of the nails (figure 3) is frequent but by no means typical of hyperthyroidism, for it is prevalent in a variety of nutritional maladies and is occasionally present in healthy individuals.

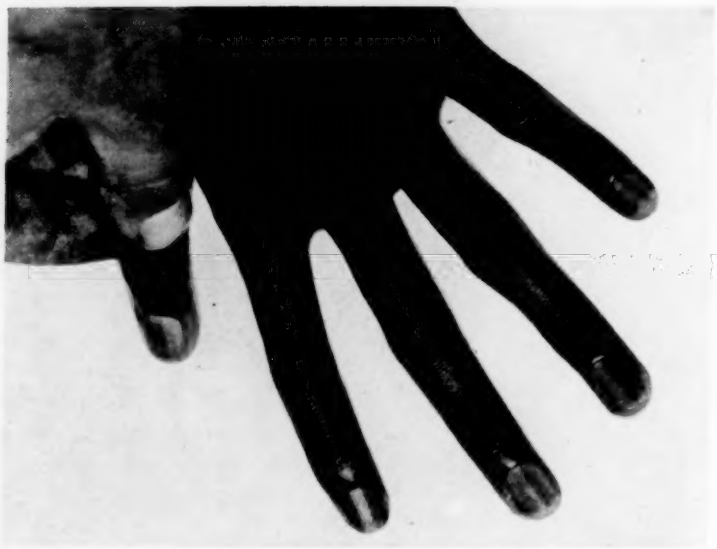

FIG. 3. Pigmented nails. See text.

The skin is peculiarly thin, the wrinkles very fine and the texture is of a velvety quality (figure 4). The skin phenomena are best observed on the back of the hands and the flexor surface of the forearms and are strikingly

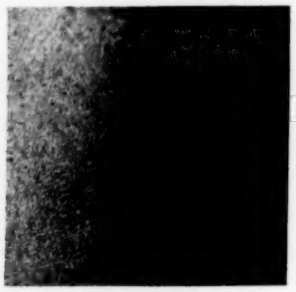

FIG. 4. Note the fine texture of the skin.

different from the dry coarse skin noted in other non-febrile nutritional maladies seen frequently in negro patients living in this section of the country.

Twenty of the 37 patients were subjected to intensive cardiovascular study with the aid of teleroentgenograms, electrocardiograms and the usual clinical methods. The data are tabulated in table 1. Of these so studied,

13, or 65 per cent showed cardiothoracic ratios greater than 50 per cent. In nine of the 13 patients who had roentgen-ray evidence of cardiac enlargement, hyperthyroidism was the only demonstrable factor responsible for the observed change. There existed neither arterial hypertension nor the phenomena of valvular disease, and all of these patients were less than 40 years of age, varying from 15 to 39 with an average age of 29 years.

Electrocardiograms were made on 22 patients (table 1). Fifteen, or

TABLE I

Case	Age	Sex	B.M.R.	Pulse Rate per Min.	Blood Pressure		Cardiothoracic Ratio	Electrocardiogram and Remarks
					Systolic	Diastolic		
1.	15	F	+97	138	130	60	55%	Electrical axis, left preponderance, high T_1, T_2 and T_3 take off.
2.	30	F	+39	156	144	84	43%	T_1, T_2, and T_3 inverted.
3.	20	F	+34	167	138	70	48%	T_2 and T_3 inverted.
4.	38	M	+38	150	134	65	59%	Auricular flutter; electrical axis, left preponderance, marked. Congestive failure, rheumatic heart disease, mitral valve, rhythm restored to normal.
5.	28	F	+60	125	120	60	57%	Electrical axis, right preponderance. Congestive failure, rheumatic heart disease, mitral stenosis.
6.	59	M	+87	128±	160	80	55%	Auricular fibrillation; electrical axis, left preponderance. Congestive failure, marked generalized arteriosclerosis, rhythm restored to normal.
7.	39	F	+47	150	155	65	56%	Auricular fibrillation; T_1 and T_2 inverted. Rhythm restored to normal.
8.	29	F	+60	132	144	60	53%	Electrical axis, left preponderance, marked.
9.	48	F	+62	112	154	80	55%	Electrical axis, left preponderance, marked.
10.	38	F	+40	125	150	80	57%	T_2 iso-electric; electrical axis, left preponderance.
11.	35	F	+36	107	150	20	54%	T_2 diphasic; electrical axis, left preponderance; rheumatic heart disease, aortic valve insufficiency.
12.	25	F	+66	125	160	70	46%	Electrical axis, left preponderance, marked.
13.	32	M	+40	115	165	65	49%	S_3 deep and notched. Electrical axis, left preponderance.
14.	33	M	+55	160±	140	60	69%	Auricular fibrillation. Congestive failure, rhythm restored to normal. P–R interval 0.24 sec.
15.	25	F	+55	118	130	75	60%	Electrical axis, left preponderance.
16.	32	F	+95	110	130	50	51%	Normal
17.	22	F	+37	115	140	80	41%	Normal
18.	39	F	+48	117	128	55	Data lacking	Normal
19.	21	F	+66	125	155	60	51%	Normal
20.	22	F	+86	140	140	70	49%	Normal
21.	23	F	+41	132	144	55	Data lacking	Normal
22.	27	F	+32	122	130	65	44%	Normal

68 per cent showed significant deviations from the normal and in only four of these did there occur vascular or endocardial disease which could reasonably have been responsible in part for the abnormal changes.

That there is a striking tendency for the heart to resume a normal functional state following relief of hyperthyroidism is clinically impressive. A study is in progress to determine whether electrocardiographic changes and cardiac enlargement disappear with the restoration of normal health.

The 15 patients who were not studied either with the roentgen-ray or the electrocardiograph varied in age from 12 to 60 with an average age of thirty-four. Six of the 15, or 40 per cent, had physical phenomena indicative of cardiac enlargement. Three of these had arterial blood pressure definitely above normal: in one 180 systolic, 112 diastolic; another 200 systolic, 124 diastolic; and another 170 systolic, 110 diastolic. All in this group maintained a sinus rhythm while in the hospital and none had the physical signs of either endocardial disease or congestive heart failure.

It is usually assumed that a low diastolic blood pressure is common in hyperthyroidism. In this group of patients with basal metabolic rates varying from plus 25 to plus 97 with an average of plus 51, the lowest diastolic blood pressure was 50 mm. Hg,* the highest 120 mm. Hg with an average of 72.05 mm. Hg. The absence of striking reductions in diastolic pressure may reflect the racial characteristics of the vascular system of the negro, for it is becoming increasingly evident that hypertension occurs at a lower age level in the negro than in the white race, and that there is a much greater tendency for the disease to run a malignant clinical course.

Thirty-four patients were treated surgically following a preliminary period of preparation. Lugol's solution, 30 drops a day, bed rest and phenobarbital, as a sedative when indicated, were the routine measures used during the pre-operative treatment. This was extended over an average period of 13 days. There were four postoperative deaths: one due to pneumonia, two to postoperative wound infection with a *Streptococcus hemolyticus* septicemia, and one a sudden death with the cause not definitely determined but attributed to pulmonary embolism.

One patient left the hospital after refusing surgical treatment. Two patients died from hyperthyroid crisis soon after entering the hospital. The total mortality was six of the 36 cases treated, a percentage of 16.6 per cent. This is an extremely high mortality, and a detailed analysis of the deaths is instructive. The death of the two patients from streptococcus septicemia was preventable and was not related directly to the hyperthyroidism.

The patient who succumbed supposedly to pneumonia two days after the operation had only five days of pre-operative iodine therapy and was operated on by a surgeon with very limited experience in thyroid disease when the basal metabolic rate was plus 61. A review of the hospital record clearly shows that postoperative hyperthyroid crisis was the immediate cause of

* Case 11 omitted due to the existence of aortic regurgitation.

death. With adequate pre-operative therapy and skilled operative technic, the operative mortality would have been only one of the 34 treated surgically, a mortality of 2.9 per cent.

It is highly significant that two patients died from the effects of acute hyperthyroid crisis before the hyperthyroidism could be controlled with iodine and before surgery was attempted. If one eliminates the clearly preventable fatal operative complications, he finds that two patients died without any attempt at surgical relief while only one died following thyroidectomy. These facts need emphasis for there are those who, because of their fear of the operative mortality, are inclined to withhold surgical therapy. In this group of patients the "medical" mortality was higher than the "surgical," if one eliminates the deaths incident to faulty surgical technic.

During the same period of time covered by this study, 71 white patients were treated for hyperthyroidism at Memorial Hospital * without a fatality. All of these had a subtotal thyroidectomy preceded by medical preparation similar to that used routinely with the negro patients. No case had, either before or after operation, a hyperthyroid crisis. This comparison clearly indicates that hyperthyroidism is a more serious problem in the negro than in the white patient, not because of a fundamental difference in the nature or severity of the disease, but rather because of delay in seeking adequate treatment.

Comments

The occurrence of hyperthyroidism in an area almost entirely free of endemic goiter is of peculiar significance for it naturally stimulates an inquiry into the causes which operate in bringing about the condition. That the factor, or factors, are potent in their effect on the negro is definitely proved by the study, for Graves' disease is proportionately as common in the negro in this area as in the white race.

If there is a difference in the reaction of the negro and the white patient to hyperthyroidism, it is probably a quantitative rather than a qualitative one for our impression is that the negro has less ability to adjust himself to the disease. This is particularly true of the cardiovascular apparatus; yet, in estimating the effects of increased metabolism on the heart, one must reckon not only with the percentage increase of oxygen requirements, but with the state of the peripheral vascular tonus and energy expenditure due to physical effort. There was not the usual lowering of diastolic blood pressure in the negro patients observed in this study, and the occupations of all the patients required more physical effort than that required in a similar group of white patients.

While these facts are undoubtedly important in exaggerating the effects of hyperthyroidism on the heart, they do not adequately explain the high percentage of significant alterations found in negro patients.

* For white patients only; similar staff at both hospitals.

The other most significant differences in the reaction to hyperthyroidism as observed in the negro are the phenomena referable to the nervous system. While the basal metabolism is elevated, restlessness, tremor and the usually observed phenomena of stimulation are characteristically evident and of great severity; yet, relief is prompt and complete as soon as the hyperthyroidism is controlled. The average patient is entirely free of all symptoms within two weeks following subtotal thyroidectomy and we have not observed a single negro patient who required a prolonged period of convalescence for the nervous system to adjust itself. This is undoubtedly an index to the nervous mechanism characteristic of the negro.

In a recent study by one of us [3] of bichloride poisoning, it was noted that there had been admitted to the Hospital Division of the Medical College of Virginia 71 patients in whom corrosive poisons had been taken with suicidal intent. There was only one negro patient in the group and she was a mulatto school teacher.

The negro is distinctly an emotional type of individual, but he has few inhibitions; hence, outlets are free and easy with the result that suicide is rare and probably for the same reason the effects of thyroxin trauma quickly disappear following the relief of hyperthyroidism.

To postulate a pathogenetic concept of Graves' disease from this study of the malady in the negro living in a non-endemic goiter area is not possible with the present lack of any common understanding concerning the real nature of the disease.

We do not believe that the "stress of modern civilization" is a factor, for, though the negro's economic stress is great, his philosophy assures complete adaptation, and emotional trauma is rarely deep or lasting in its effect.

The rarity of endemic goiter in this area quite definitely outlaws the idea of an absolute iodine deficiency as an important etiological factor. The more recent observations of Marine [4-14] strongly indicate that diet can and may be a significant factor in the pathogenesis of the Graves' syndrome. From this study it is not reasonable to suggest what nutritional factors, if any, operated in the production of exophthalmic goiter in the negro living in a geographic area where endemic goiter is rare, yet, the probability of such an etiological factor is intriguing.

In the negro patients seen in the Out-Patient Clinic and hospital wards there are prevalent quite evident nutritional defects which are traceable to a diet high in carbohydrates, not adequately supplied with complete proteins and milk, woefully lacking in vegetables and fruits, and frequently deficient in total calories. Though this be true, it is not possible to assemble even circumstantial evidence incriminating any specific essential food deficiency. In the final solution of the pathogenesis of exophthalmic goiter, it is probable that many factors will be found that operate jointly in precipitating the syndrome. It is certain that iodine deficiency and the trauma of "modern life" are not the sole factors concerned.

Conclusions

1. Hyperthyroidism is a relatively common malady in the negro living in this geographical area.

2. The disease manifests itself clinically as typical Graves' disease and is accompanied by a diffuse hyperplasia of the thyroid gland.

3. The cutaneous changes are of peculiar interest and of real diagnostic importance.

4. The cardiovascular apparatus of the negro patient suffers greatly from the effects of hyperthyroidism largely because of delay in seeking adequate treatment.

5. Some factors other than primary iodine deficiency or the stress of urban life must be found to explain adequately the pathogenesis of exophthalmic goiter. This study leaves the question of specific etiology unanswered.

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THE ACUTE AND SUBACUTE PULMONARY INVOLVEMENT IN RHEUMATIC FEVER WITH NOTES ON THE COMPLICATION OF BASAL PULMONARY COLLAPSE*

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THERE has been in recent years a renewed interest in the pulmonary lesions of rheumatic fever. Rabinowitz [1] (1926), basing his opinion upon clinical data, felt that there was a distinct rheumatic pneumopathy. In conjunction with Eiman, in 1927, we described certain previously unrecorded gross and histologic pulmonary lesions occurring in rheumatic fever,[2] and we elaborated upon these in 1932.[3] We concluded that pulmonary involvement in rheumatic fever was common and the changes specific. In the meantime, other reports appeared in England (Naish, 1928 [4]; Fraser,[5] 1930), based on independent observations and with similar conclusions.

We judge by the references that come to our attention that the view that rheumatic fever involves the lungs and produces characteristic changes is being more and more widely held, though this view is by no means universal. Our own continued study of this subject, both clinical and pathologic, has increased our conviction that such is the case and that involvement of the lung to some degree in rheumatic fever is as common as that of the heart. We further feel that the acute pulmonary changes lead to permanent alterations and that the latter play a very important rôle in the strain and ultimate defeat of the right ventricle, which has heretofore been ascribed to the mechanical influence of mitral stenosis alone. We hope soon to present the evidence for this belief.

If this conception of the influence of the rheumatic pulmonary lesions on the course of rheumatic heart disease be eventually borne out, it is obvious that the rheumatic pneumopathies will take on a very important aspect. With this in mind, we wish to review the clinical picture caused by the acute lesions, to compare it with that of other common lung inflammations, from which it differs considerably, and also to add a brief comment on an interesting complication that develops in the acute and subacute phases, namely, an "inflammatory collapse" of lung tissue. Our concept of the clinical picture of the rheumatic pneumopathy has been formed by study of more than 25 patients, in whom necropsy revealed cardiac and pulmonary lesions. The pathologic changes are similar to those described in previous articles and will not be discussed here.

The degree and extent of pulmonary inflammation vary greatly with a correspondingly wide variation in the clinical picture. It is an interstitial

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inflammation, which in severe involvement is accompanied by alveolar exudate giving rise to frank consolidation; the physical signs are then indicative of pneumonia. In the majority of cases, the involvement is moderate to slight, the interstitial pneumonitis being less intense, confined to smaller areas and accompanied by little and patchy alveolar consolidation. In such cases the physical signs are less conspicuous and often the pulmonary lesion is revealed only by necropsy.

Lung involvement usually appears shortly after the onset of polyarthritis, occasionally precedes it, and in many instances, especially in children, it may dominate the clinical picture from the beginning, the arthritic phenomena being slight or indeed entirely absent. In such cases the latter development of pericarditis and endocarditis will reveal the rheumatic nature of the infection. This type of pneumonia does not depend upon the presence of bronchitis after the fashion of ordinary bronchopneumonia but will often follow as do the other types of acute rheumatism, shortly after the development of sinusitis, nasopharyngitis, and tonsillitis, as a part of the widespread systemic reaction to streptococcic infection.[6] It should not be regarded as a complication of rheumatic fever; rather is it an integral part of that disease, as much so as endocarditis.

The Clinical Picture of Rheumatic Pneumonia and Pneumonitis. The pulmonary involvement is usually insidious, there being little in the appearance of many patients that would direct the physician's attention to the possible existence of pneumonia. Examination of the lungs will often reveal not only in children and adolescents, but also not infrequently in adults with acute rheumatic fever, areas of bronchial breathing and dullness on percussion, suggestive of consolidation. The bronchial breathing is sometimes loud, at other times muffled and distant; in some patients expiration lacks the exquisite high pitch heard over the consolidation of pneumococcus lobar pneumonia. So-called acute emphysema will sometimes be present, due to an acute inflammatory turgescence of the lung tissue. These signs are best elicited posteriorly over the lower lobes; they are often conspicuous at the angle of the scapula, and to a lesser degree are found in the axillary areas. The upper lobes are not immune to involvement. Where bronchial breathing is pronounced, egophony and whispered pectoriloquy may be noted. Râles may or may not be present; they are of variable quality, and are seldom heard in the same number and intensity as in pneumococcus lobar pneumonia. There are, however, occasional cases in which the physical signs of consolidation are almost identical with those found in pneumococcus pneumonia. The similarity exists for only a short time because the transient character of the rheumatic lesion is in striking contrast to the orderly and progressive resolution of the pneumococcus consolidation. What on one day appears to be characteristic consolidation with tubular breathing may appear within the next day or two as an atelectasis with very distant tubular breathing or often with an absence of breath sounds. The signs of con-

solidation may appear in another lobe; in some patients the successive involvement and abatement in a number of areas suggest an analogy to the course of the polyarthritis. Consolidation may recur in the same area within a few weeks in virulent cases. In many patients the physical signs of pulmonary involvement, while unmistakable, suggest that the inflammatory reaction has not gone on to true consolidation since typical bronchial

FIG. 1. Right lung from a case of rheumatic pneumonitis, subacute stage showing basal collapse. Note marked diminution in size of the lower lobe. There was a small effusion in both pleural sacs and an acute pericarditis with 250 c.c. of exudate. The effect of the latter on the production of a right sided collapse was probably negligible.

breathing is absent—indeed more frequently the breath sounds are distant or obscured by râles. In such cases the term " pneumonitis " will be preferred by many physicians. This milder degree of involvement is probably that which is most commonly encountered.

There is a surprising disproportion in most cases between the symptoms and the physical signs, even when the pulmonary involvement is fairly extensive. A comparison with the clinical course of pneumococcus lobar pneu-

monia will emphasize this point. The classical picture of lobar pneumonia calls for an initial chill, prolonged and high fever, usually severe pleural pain, rusty sputum, marked elevation of the respiratory rate and crisis; these are not observed in rheumatic pneumonia and their absence is largely the reason for the tardy recognition of an important clinical phenomenon. The initial chill that signalizes the onset of pulmonary invasion has not been noted, or at least is not striking enough to achieve distinction from the mild chilliness that recurs from day to day in some rheumatic fever patients. There may

FIG. 2. Lobular atelectasis developing in the course of acute interstitial rheumatic pneumonitis (× 33).

or may not be a cough; if present it is rarely troublesome, and never very productive. In some cases, the sputum is blood streaked, which may be ascribed by the attending physician to passive congestion secondary to cardiac failure, though it probably has its origin in the hemorrhagic alveolar exudate of the pneumonia. The sputum does not present any special bacteriological findings. Pneumococci may be found, but not as a predominant organism; streptococci, both of the hemolytic and of the viridans strains, will often be present. Such findings may represent only the bacterial flora

of the nasopharyngeal sinus or tonsillar infection; few organisms, often none at all, are found in the inflamed lung tissue.

The absence of respiratory distress in most patients is striking. Expiratory grunt and the play of the nostrils, common in lobar pneumonia, are seldom present. The respiratory rate is slightly or moderately elevated, irregularly so. This is all the more remarkable in view of the fact that a serious myocarditis often coexists. In occasional cases where both lungs

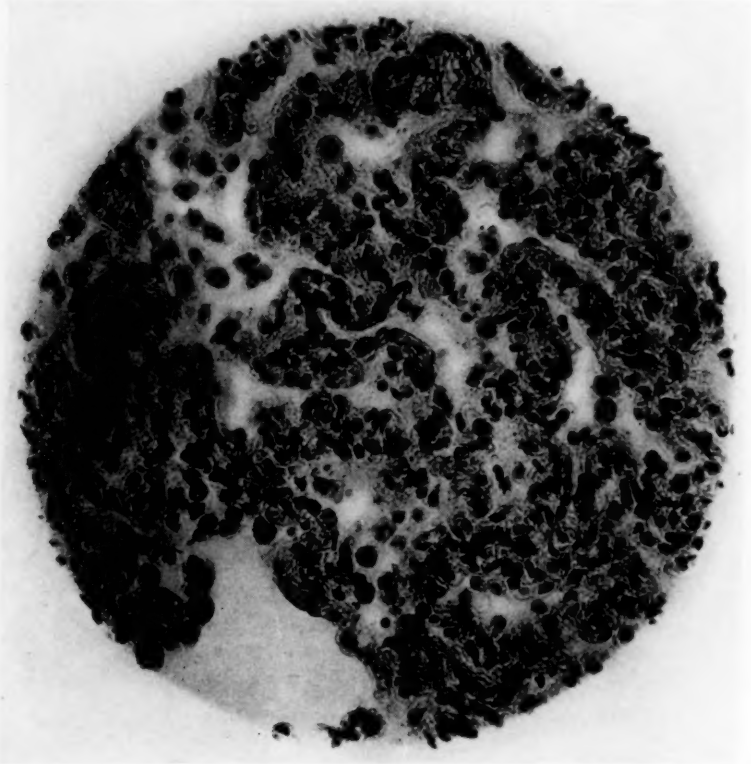

FIG. 3. Early congestive phase of acute interstitial pneumonitis showing marked capillary congestion, early interstitial infiltration of endothelial cells and beginning collapse. There was no obstructive change in the bronchial tree (× 276).

are almost entirely consolidated, the respiratory rate will quickly rise in what usually develops to be a terminal phase.

Pleural pain is relatively rare. Most patients never complain of it, but, in contrast, a considerable number have substernal pain due to pericarditis. Fibrinous pleurisy, often observed at necropsy,[7] has been accorded a degree of importance in the literature which is not altogether warranted by its observable clinical manifestations. While friction rubs are not uncommon, pleural pain, curiously enough, has been encountered only in the minority of patients with pulmonary consolidation. In only two instances in a series of

25 patients was lancinating pleural pain the striking initial feature—as it so commonly is in pneumococcus pneumonia. Empyema as a direct complication has not been present either clinically or in the cases that we have seen at necropsy. Its rarity in rheumatic fever was pointed out many years ago by Longstreth.* [8]

The fever is usually moderate, in some instances high, but very irregular

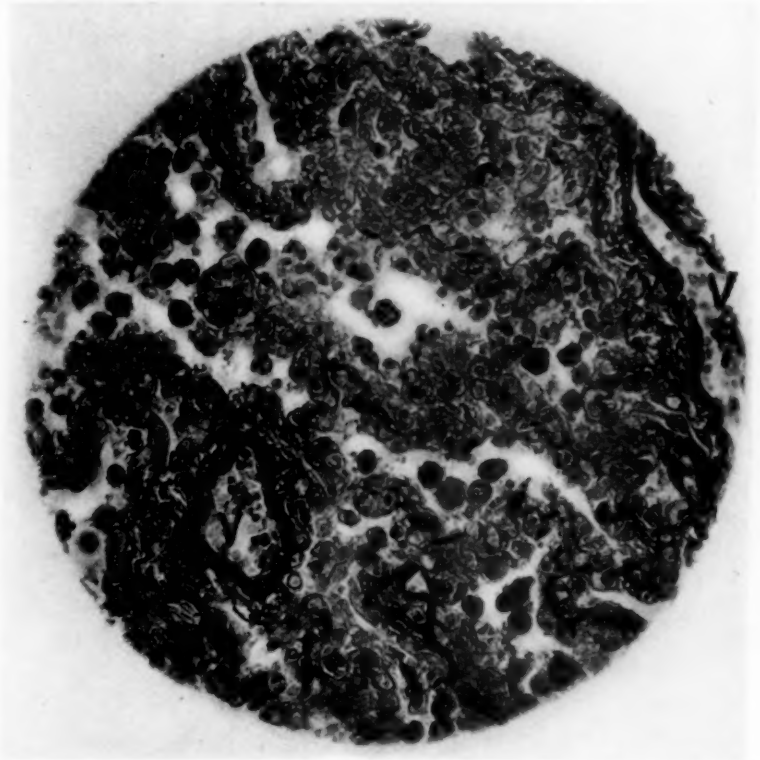

FIG. 4. Showing early acute interstitial rheumatic pneumonitis and beginning collapse. Note acute destruction of the elastica; it is preserved in the walls of the small veins (V) but has practically disappeared from the interstitial alveolar structure, a few dark stained shreds and granules remaining (Weigert stain) (× 276).

(102 to 105°), and probably related to the systemic infection rather than to the local pulmonary changes. Our experience does not coincide with that of Naish who was impressed by the minor character of the febrile elevation in most of his caess. It is possible that salicylate therapy may have been partly responsible for this difference; usually the presence of marked pulmonary involvement is associated with a severe type of infection, in which the febrile reaction is considerable. There is no crisis; the fever follows the

* Morris Longstreth, Pathologist (1872–1879) and Visiting Physician to the Pennsylvania Hospital (1879–1895).

irregular course seen in such severe cases, and gradually falls in proportion to the general recovery from the rheumatic disease.

In most cases the pulmonary involvement is obscured by the generally severe symptom complex that is known as acute rheumatic fever, and apparently adds little to the already existent toxicity. There is a small group of patients in whom the pulmonary invasion is extremely rapid and widespread, accompanied by quickly developing dyspnea and cyanosis. In such

FIG. 5. Showing subchronic interstitial rheumatic pneumonitis complicated by excessive interstitial fibrosis in a collapsed area. It is doubtful whether such lung tissue can ever regain its pre-inflammatory resiliency (× 276).

instances the pulmonary involvement can suddenly alter the prognosis and can be regarded as the actual cause of death.

The rheumatic and the pneumococcic pneumonias can co-exist in the same lung, but our necropsy experience suggests that such occurrence is distinctly uncommon. The ordinary type of bronchopneumonia may co-exist or occur as a secondary infection, but this association is also, we think, uncommon. The large majority of rheumatic fever patients with lung involvement do not have a history of preceding bronchitis, nor do they have

the purulent expectoration or diffuse bronchial moisture usually noted in cases of suppurative bronchitis or the common type of bronchopneumonia.

Laboratory Data. The laboratory data differ in no way from those usually recorded in rheumatic fever, namely, a leukocytosis of 10,000 or more, occasionally mounting as high as 25,000; the differential count usually shows a moderate increase in both neutrophiles and monocytes. Blood cultures were done in only a few cases and were always negative.

Roentgen-ray examination of the chest is often disappointing. Areas of moderately increased opacity (mild cloudiness of lung fields) without well defined borders are often interpreted as passive congestion. These patients usually do not have marked congestive heart failure. Where there has been opportunity to repeat the roentgenogram within a few days there has been noted in a few instances, rapid spread and regression of this haziness, corroborating the transient changes noted clinically in the same patients. There is a remarkable example of a complete subsidence within four days pictured in Poynton and Schlesinger's [9] text "Advances in the Study of Rheumatism" (1931). The attending physician refused to believe that a pneumonia could so completely subside in such short time.

The Subclinical Pulmonary Involvement of Rheumatic Fever. It can safely be said that the majority of moderately ill rheumatic fever patients will not show anything like the striking physical signs of consolidation or of widespread pneumonitis. With increasing evidence of the importance of the pulmonary lesions, however, more complete examination should be attempted and fleeting changes will possibly be detected in many milder cases of rheumatic fever. Moderately impaired breath sounds, slightly to moderately impaired percussion note and possibly a few râles will constitute the "subclinical" lung signs, very brief and not very convincing, yet probably of great importance in the subsequent clinical course of cardio-pulmonary dysfunction. These statements are based on the fact that many patients with negative chest findings in the ordinary routine examination present slight to moderate pneumonitis of the characteristic type at necropsy; in fact, the incidence of pneumonitis in some degree is almost the same as that of myocarditis.

"Inflammatory Collapse"—A Complication of Rheumatic Pneumonia and Pneumonitis. The physical signs of consolidation may disappear rapidly in the course of a few days and are not infrequently followed by dullness and impaired or absent breath sounds at the bases. These latter signs may have been present from the beginning. At any rate they persist for many days, even weeks, and are due to pulmonary collapse or atelectasis, usually accompanied by small pleural effusions. This collapse has been noted frequently on the left side and is currently attributed to atelectasis secondary to pericardial effusion. Coombs [10] ascribed it to reflex immobilization of the left diaphragm following pericarditis; we have seen it as a right sided lesion in the absence of pericarditis. Naish suggested that the

constant friction caused by the pulsating heart probably dictated the development of primary inflammation in the adjacent left lung but he rejected the older theory of cardiac pressure with subsequent pulmonary collapse. Possibly a number of factors operate, namely the small to moderate pleural effusions that often accompany the atelectasis, the prolonged confinement to bed with its subsequent diminution of pulmonary function, and probably in some instances, a reflex inhibition of diaphragmatic activity as postulated by Coombs. However, these possible factors do not afford a sufficiently reasonable explanation in the majority of cases. The pleural effusions are usually too small and sometimes absent, as shown at necropsy, and certainly are not to be compared with the massive hydrothorax of chronic congestive heart failure where the atelectasis is less striking in extent.

The most important factor we believe is the pneumonia or pneumonitis per se. Basal collapse can be seen not infrequently in conditions other than rheumatic fever, for example, in senile emphysema in conjunction with pleural effusion. (We exclude from consideration the ordinary types of atelectasis: the bronchial obstructive and the compressive.) Evidently the resiliency of the lung tissue is a factor in the development of basal collapse. Following rheumatic pneumonia, there is a distinct loss of the normal elasticity of the parenchyma, a direct result of the " fibrinoid " degeneration of the alveolar walls, with the destruction of the elastic and reticular fibers of the interstitial framework. There is finally a replacement by an interstitial fibrosis in which there is usually a marked regenerative hyperplasia of coarse, irregular and fragmented elastic fibers, the net result of which is not a return to the normal elastic state but a lung tissue that is much firmer, with rubberoid consistency. Where the loss of the elastica has been great and respiratory function temporarily destroyed, the inflammatory congestion marked and air-absorption facilitated, collapse fibrosis is apt to occur. Since the incidence of rheumatic pneumonitis is greatest in the lower lobes, they are the favored site for the development of this lesion. Moreover, those factors which we believe to be of secondary importance, namely, pleural effusion and pericardial effusion will exert their influence largely on the lower lobes. Collapse may involve an entire lobe or a portion of it, and it follows from the foregoing statements that such gross involvement is almost always basal; the collapse, however, may be of lesser proportions, giving rise to small lobular atelectases; we have noted instances of lobular atelectasis in the upper lobes, a location practically immune to the influence of pleural effusion.

The lesion may be termed " inflammatory collapse " in contra-distinction to the mechanical types produced by either external compression or bronchial obstruction. The physical signs of basal dullness and impaired breath sounds often noted even late in convalescence from a severe attack of rheumatic fever, are typical of this lesion. Coarse râles differing from those heard earlier in the state of intra-alveolar consolidation also may persist for

many days or weeks and can be ascribed to a plastic pleural reaction. Whether consolidation necessarily preceded this state or whether severe grades of pneumonitis, short of actual consolidation may equally lead to this same result, cannot be stated with any certainty. Roentgenograms may reveal elevation of the diaphragm on one or both sides, with or without small pleural effusions. "Hypoventilation" of the lungs due to elevation of the diaphragm is a diagnosis occasionally made by the roentgenologist.

It is questionable whether the function of such collapsed lung tissue can ever return to normal. In a case recently seen at necropsy, the lower right lobe was still considerably shrunken in size two months after the diagnosis of rheumatic pneumonitis had been made. We have no later direct observations on this point, but inasmuch as the interstitial fibrosis that follows rheumatic pneumonitis will in all likelihood be exaggerated in areas that were collapsed, it is reasonable to assume that respiratory function will remain impaired in spite of re-aeration. It is believed that respiratory exchange is diminished in areas of interstitial pulmonary fibrosis (the state known in the German literature as "pneumonose").[11, 12, 13]

The Probable Relationship of Ewart's Sign (of Pericardial Effusion)[14] to Rheumatic Pneumonia and Inflammatory Collapse.* Bronchial breathing suggestive of consolidation is not infrequently found at the angle of the left scapula, due it is claimed to an atelectasis secondary to pericardial effusion rather than to pneumonia. This is an old observation known as Ewart's sign. It is significant that while this sign is encountered in the great majority of instances in young patients with rheumatic fever, much greater effusions noted occasionally with tuberculous pericarditis do not produce identical signs of "false" consolidation.

We have had ample opportunity to study sections from atelectatic left lungs in acute rheumatic fever with pericarditis. Such sections show a pneumonitis, a definite inflammatory reaction similar to the pneumonia or pneumonitis encountered in the right lobe, of the same patient if such a localization has developed, or in the right lung of other patients. The tendency to collapse in rheumatic pneumonitis, described in earlier paragraphs as due to the impaired elasticity and destruction of normal interstitial connective tissue, is the probable basis of Ewart's sign. Lung tissue so involved is probably vulnerable to pressure from any direction; if this assumption is correct, then pressure exerted by pericardial effusion merely hastens and accentuates the signs of a pulmonary inflammation already present.

Summary

Pulmonary consolidation constituting a true pneumonia is often seen in severe cases of rheumatic fever; a lesser degree of lung involvement, not

*Ewart listed ten signs of pericardial effusion, of which the eighth dealt with "the posterior pericardial patch of dullness," a sign previously noted by Bamberger (1867), Pins (1889), and Samson (1892); the tenth was the "posterior pericardial patch of tubular breathing and egophony" which has been combined by usage with the eighth sign as Ewart's sign of pericardial effusion.

actual consolidation, preferably termed "pneumonitis," is frequently encountered. These changes are not secondary complications but an integral part of the disease. The clinical manifestations are often overlooked because of the transient character of the consolidations and the inability to examine the bases of the lungs of patients wracked with arthritic pain.

In most patients with rheumatic pneumonia there is a characteristic disproportion between symptoms and physical signs, the latter being the most striking. Respiratory distress is comparatively slight but becomes marked when pulmonary involvement is almost complete. The acute inflammation is followed in some cases by a characteristic "inflammatory collapse," usually basal; the main factors appear to be a loss of elasticity, air-absorption, and subsequent contracture due to interstitial pneumonitis.

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THE NECESSITY OF CERTAIN CRITERIA FOR THE DIAGNOSIS AND CURE OF RHEUMATOID ARTHRITIS *

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Perhaps the most important problem which confronts a young medical organization such as the American Rheumatism Association is the proper orientation of the Society in the field which it proposes to cover. This question has already been attacked in part by this group. In the first place we decided that we would not confine ourselves strictly to the matter of arthritis, but would cover the whole field of rheumatism, including rheumatic fever. Our next task is to attack the problem of nomenclature, and what a difficult problem it is! The English have already made a brave effort in this direction, and their achievements are covered in the report of the Sub-Committee on Nomenclature of the National Rheumatism Committee, which was appointed by the Royal College of Physicians. In our own country the American Heart Society has set us a fine example in their classification and nomenclature of diseases of the heart. This subject is much too large to be covered by a president's address. Today I simply wish to point out the necessity of establishing certain criteria for the identification of rheumatoid arthritis, a disease which might well be called the key-stone of our problem. I shall also say something concerning the criteria essential for the pronouncement of cure in this disease.

Rheumatoid arthritis is one of the great diseases of medicine. With tuberculosis and syphilis it constitutes the great triad of chronic granulomatous infections prevalent in our climate. This fact in itself would help to explain the rapidly growing interest in chronic arthritis, and in rheumatoid arthritis in particular. But there is an even stronger reason for the increasing interest in rheumatoid arthritis. It is one of the few remaining unsolved problems in the field of infectious diseases. To be sure, there are many things we do not understand about tuberculosis, syphilis, pneumonia, and other infectious diseases, but at least we know their causes. In the case of rheumatoid arthritis we are still debating the etiology, and much work remains to be done before this problem can be settled. Etiology, however, is only one of the many problems connected with rheumatoid arthritis. We must learn more about the influence of heredity and other predisposing factors such as climate, constitution, malnutrition, avitaminosis, etc. And finally, we must learn how to treat the disease successfully. We might say that rheumatoid arthritis today stands in the same position that tuberculosis occupied 60 or 70 years ago before Robert Koch discovered the tubercle bacillus. Rheumatoid arthritis is waiting for its Robert Koch, and I for

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one believe that within the next 10 years he will probably make his appearance.

Before taking up in detail the criteria which are necessary for the diagnosis of rheumatoid arthritis, let us review briefly the classification of the British National Committee.[1] Under the heading of "rheumatoid arthritis" we find the following subdivisions:

(1) Rheumatoid arthritis with associated factors. Under this heading are placed metastatic or focal arthritis, including so-called multiple infectious arthritis; in other words, the rheumatoid type of arthritis closely associated clinically with focal infection. Under the same heading the English classifiers place rheumatoid arthritis associated with the disordered metabolism of the menopause—a rather dubious effort to tie up the disease with another well recognized pathologic condition.

(2) Rheumatoid arthritis with no known associated factors. Under this heading the British include the classic type of rheumatoid arthritis as it is seen in women during the child-bearing period. I might add that it is also seen at this time of life in men even though they do not bear children. Under this heading the British also include Still's disease, or the rheumatoid arthritis of children. The British Committee then draw a "deadly parallel" between rheumatoid arthritis with known associated factors and rheumatoid arthritis with no known associated factors, and attempt to make a clinical distinction between the two groups. The differentiation occupies more than four pages of text, the reading of which does not convince one that such a differentiation is feasible or desirable. About the only real difference between the two groups is that the first group is associated with definite focal infection whereas in the second group no focus of infection is demonstrable, but we all know how frequently foci of infection can be missed, even after the most careful study, and we also know that on the other hand teeth, tonsils, and sinuses are often blamed for crimes which they did not commit. Therefore, it seems to me that this differentiation of rheumatoid arthritis into two groups, while intriguing, is not justified. So far as we have been able to make out from our studies, both types present the same pathological and clinical manifestations, and the immune responses are the same for both groups. For the time being, therefore, I suggest that in America we continue to look upon rheumatoid arthritis as a single disease and that we attempt to establish certain criteria for its identification.

In discussing the necessary criteria for the diagnosis of rheumatoid arthritis, we may divide them into pathological, clinical, radiological, and serological findings.

1. The pathological criteria are quite definite, but unfortunately are not obtainable except by means of a biopsy. In a certain number of cases a synovectomy may be indicated and tissue becomes available for microscopic study. The gross pathology of the joint is not sufficiently characteristic. It might be simulated by some other form of joint infection, particularly the

gonococcal joint. Microscopically, a vascular granulation tissue containing collections of lymphoid cells which often resemble true lymphoid follicles, presents a picture which in my experience, one never sees except in rheumatoid arthritis. If a subcutaneous nodule presents itself it can readily be removed, and again microscopic study reveals the characteristic histologic changes so well described by numerous pathologists. As pointed out by Dawson,[2] these changes do not differ widely from those observed in the subcutaneous nodules of rheumatic fever. However, the nodules of rheumatoid arthritis are usually larger than those of rheumatic fever, and not so likely to appear and disappear.

2. *Clinical Criteria.* The clinical criteria of rheumatoid arthritis are perhaps the most important of all, and of these, the most characteristic is the fusiform finger. Periarticular swelling is of course a feature of any form of joint infection, but the peculiar, doughy enlargement of the proximal interphalangeal joints of the fingers is the outstanding badge of rheumatoid arthritis. The fusiform finger usually appears early in the disease and may persist for years. Eventually however, as the disease passes into the inactive stage, the swelling in large part disappears and is replaced by ankylosis and deformity. Closely associated with the fusiform swelling of the fingers, and almost as frequent is a swelling of several knuckles, which when accompanied by atrophy of the interossei muscles, gives the hand its characteristic appearance.

The second clinical criterion is the multiplicity of joints involved. The disease is still often spoken of as chronic multiple arthritis. It is indeed rare to see only one joint affected. I recall in my practice one young woman who showed a fusiform swelling of the index finger of the left hand. She was a slender under-nourished girl of 23 years, and I fully expected to see the disease extend eventually to other joints. However, no other joints were ever involved during the two years or more that she was under my observation. During that time the swelling of the finger remained practically unchanged. I was suspicious of tuberculosis in this case, but it could not be proved by roentgen-ray or other diagnostic methods. In discussing the characteristic lesions of the hands and fingers in this disease, I am tempted to include the frequent involvement of the wrists and particularly their early tendency to ankylosis. However, this could hardly be looked upon as one of the essential criteria; neither could the vasomotor disturbances of the hands and feet, though I always expect the rheumatoid arthritic to greet me with the cold, clammy hand so typical of the disease. The wasting of the muscles and the atrophy of the skin and subcutaneous tissues are seen in other forms of infectious arthritis as well as in the rheumatoid type. There are other favorite sites of rheumatoid manifestation, particularly the knees, feet, elbows, and cervical spine. I have never been able to understand why the hips and the toes so frequently escape involvement.

I have already referred to the highly characteristic subcutaneous nodule. When present, it is almost pathognomonic of the disease, but unfortunately it occurs in only 4 or 5 per cent of cases. Certain other clinical phenomena, such as iritis, psoriasis and the various forms of erythema, are frequently associated with rheumatoid arthritis, but could in no sense be considered as criteria of the disease.

Should the physician ever make a diagnosis of rheumatoid arthritis in the entire absence of swelling or deformity of the joints? Only rarely would such a diagnosis be justified, though one might be strongly suspicious of what I often call the pre-arthritic stage of the disease.

3. *Radiographic Criteria.* The roentgen-ray appearance of the bones and joints in rheumatoid arthritis is highly characteristic, so much so that it is usually possible to make a diagnosis of the disease by this means alone. In the very early stages there are no typical manifestations. Soon, however, the roentgen-rays begin to show the characteristic decalcification of the bones and the soft tissue swelling. As the disease progresses there is narrowing of the inter-articular space due to thinning of the cartilage, and blurring of the whole joint architecture. Several writers have stressed the peculiar punched-out areas, which are a prominent feature of rheumatoid arthritis, and occur just as frequently in this disease as in gout. In the latter disease, however, the punched-out areas are much larger than those in rheumatoid arthritis. In the final stages of rheumatoid arthritis the joint surfaces may become fused through fibrous or bony ankylosis, and in deformed joints there may be subluxation or dislocation. In the late stages hypertrophic changes may be observed, but this should not lead to confusion of the disease with osteo-arthritis.

Can a definite diagnosis of rheumatoid arthritis be made from the roentgen-ray pictures alone? In very early cases, no. In well established cases, yes, in a high percentage of cases. Occasionally, a gonococcal arthritis might be a source of error, but the anamnesia and other clinical data would prevent a mistake in diagnosis.

4. *Serological Criteria.* The most characteristic blood change in rheumatoid arthritis is the agglutination of the *Streptococcus hemolyticus* by the patient's serum, usually in high dilutions. This test is positive in a large proportion of cases, the actual percentage of positive reactions depending on the duration of the disease. In early cases the presence of agglutinins is not so conspicuous a finding, but in the original report which the writer made with Nicholls and Stainsby in 1931,[3] we obtained a positive agglutination reaction in 97 per cent of 153 cases of well established rheumatoid arthritis. Dawson, Olmstead and Boots[4] demonstrated the presence of streptococcal agglutinins in 67 per cent of their series; Blair and Hallman,[5] in 85 per cent of their patients.

We may conclude then that while a positive streptococcal agglutination reaction is present in a high percentage of cases of rheumatoid arthritis, it

is not invariably present. It may be said, however, that a positive agglutination reaction is strongly confirmatory of rheumatoid arthritis and should be looked upon as one of the important diagnostic criteria.

Other immunological phenomena have been noted in the serums of patients with rheumatoid arthritis. I refer to the ability of rheumatoid sera to precipitate the various group specific fractions of the *Streptococcus hemolyticus* and to the presence of anti-streptolysin in the sera of some patients with this disease. Neither of these antibodies, however, is so consistently present as are the agglutinins. For this reason they could not be looked upon as important criteria in the diagnosis of the disease.

Another reaction of considerable importance is the sedimentation rate of the red blood cells. The sedimentation rate shows sharp acceleration in practically 100 per cent of cases of rheumatoid arthritis during the active stage of the disease. This test of course does not differentiate rheumatoid arthritis from other forms of infectious arthritis. However, a rapid sedimentation rate is an important feature of the disease.

A moderate grade of leukocytosis, with some increase in the percentage of immature cells, is seen in a good many cases, but is not a constant enough finding to be dependable. The same is true of the secondary anemia which so frequently accompanies the disease.

Summarizing then, we may say that a patient with rheumatoid arthritis should present the picture of a chronic progressive multiple arthritis characterized in its earlier phases by soft tissue swelling, and in its later stages by some ankylosis and deformity. Implication of the interphalangeal, metacarpophalangeal and wrist joints is especially characteristic. The synovial membrane and the subcutaneous nodules, when present, show specific histological changes. The radiographic evidence is quite typical, and the patient's serum in a large majority of cases will induce an agglutination of the streptococcus hemolyticus. A rapid sedimentation rate of the red blood cells is highly characteristic, but is seen in other forms of infectious arthritis as well.

Let us now turn our attention for a few moments to the question of criteria for determining the cure of rheumatoid arthritis. Such criteria are obviously needed and should serve as a guide to any of our members who report on the effects of this or that remedy in the treatment of the disease. There are entirely too many articles being written on the treatment of rheumatoid arthritis. Most of them fail to take into account the natural tendency of the disease to remissions and exacerbations, and the writers are too content to state that such and such a percentage of patients were "improved" by the treatment under consideration. Personally I will not be permanently satisfied with any remedy for arthritis which merely improves the patient. We must strive for a *cure,* something that will give the patient complete and permanent relief from the disease. When should we be willing to pronounce the rheumatoid patient cured? I should say that the first

requirement would be: clinical cure evidenced by freedom from pain and swelling of the joints and partial or complete return of joint function. In addition to freedom from joint symptoms the patient should feel well and should be entirely relieved of the exhaustion and fatigability which so frequently accompany the disease. At this point, however, we must make certain qualifications in our criteria. It is true that cure in an early case frees the patient from practically all earmarks of the disease. In those comparatively rare instances, however, where a well-established arthritic recovers from the disease a number of scars may remain. The patient returns to normal health and the joints are free of swelling and pain; but there may be some residual enlargement. Ankylosis and deformity may persist in certain joints, but the patient does not mind this when he feels so well in all other respects.

In a cured case the sedimentation rate of the red cells should return to normal, and the specific agglutinins for the hemolytic streptococcus should disappear from the patient's serum. The leukocyte count returns to normal, and the secondary anemia is replaced by a normal blood count.

Roentgen-ray pictures may reveal certain residual damage to several of the joints, but in early cases radiographs may show little or no evidence of permanent joint damage.

The patient should not be looked upon as a cure until he has remained free of symptoms for at least one to two years.

Would it not be worth while for this Society to appoint a committee whose duty it could be to set up certain criteria for the diagnosis and cure of rheumatoid arthritis? The acceptance of such criteria by the members of this group would, in my opinion, greatly advance the cause of efficient therapy. When the curative effects of the numerous types of therapy were analyzed with such criteria in mind, perhaps fewer but more intelligible contributions to the literature of rheumatism treatment would be made.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

METABOLIC STUDIES IN A MAN WHO LIVED FOR YEARS ON A MINIMUM PROTEIN DIET*

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I have on several occasions had the opportunity of coöperating in making interesting studies of persons who voluntarily carried out with great care and devotion a one-sided extreme diet. Such were the final studies by Dr. E. F. DuBois,[1] upon Dr. V. Stefansson and K. Andersen, both of whom had lived for a long time exclusively upon meat and fat and the internal organs of butchered animals. We were able also in 1933 and later to carry out observations on a well known nutritional physiologist, Dr. C. Röse, who for 15 years investigated the question of the minimum protein requirement, the protein optimum, the biological value of single varieties of protein and other related problems.

In the study of problems of nutrition, protein, the most important and indispensable of foodstuffs, has been the repeated object of investigation. The literature concerning this substance is almost too great for review, and many questions here seem to be still unexplained. It would be far beyond the limits of this paper to present even a partially comprehensive survey of this problem. The collected literature may be found in the papers of Heupke,[2] Hindhede, and Süsskind.[3] I should like to limit myself to a few questions which I have studied in association with Dr. C. Röse in the last few years, namely, the question of efficiency on a protein poor diet, the total metabolism at the borderline of minimum protein requirement, and the specific dynamic protein effect after feeding varieties of protein of different biological value in varying amounts.

Since there is a want of clearness in the literature concerning the minimum protein requirement, I should like first to briefly define protein minimum. We understand by the minimal nitrogen excretion, which was termed by Rubner the wear and tear quota, the smallest or lowest nitrogen excretion values in an individual on a protein free diet. The physiological protein minimum is found when the minimal nitrogen balance is reached, i.e., when output and intake balance one another. The physiological protein minimum is independent of the kind of protein, the state of nutrition or other factors. It is necessary in the technic of the investigation, not only that an analysis be made of the excretions (feces and urine) and of the perspiration and secretions of the skin, but also that there be an exact determination of the composition of the diet which is fed. Differences from table values by as much as 50 per cent may occur. Months or years of prolonged series of

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diets with similar foodstuffs presuppose, if the conclusions are to be clear and unequivocal, a continuous analysis of the single basic foods, such as potatoes, milk, bread, etc. We have carried out these analyses.

Factors which influence the minimal nitrogen excretion are, aside from those already mentioned, the compatibility of the usually very onesidedly constructed diet, vitamins, the amount of fluid, the state of nutrition, the time of life, the acid base balance, and the biological value (quantivalence) of the single varieties of protein.

The very question of the acid base economy is still a much debated question, in connection with which Röse, R. Berg and others have developed a special point of view. The richness in base of the diet and the previous output of acid are of decisive importance in the question of the minimal protein requirement. In careful metabolic studies Röse has recently tested again the relation between minimum protein requirement and the base content of human food. In a preliminary period, with a protein intake of 28.17 gm. daily and the addition of basic salt, he found a nitrogen storage of 0.60 gm. The urine was alkaline at this time. In the main period he left out the basic salt, keeping the amount of protein the same, with an exactly similar diet. The urine became acid and the loss of nitrogen amounted to 0.44 gm. If he then added basic substances, a storage of 0.155 gm. of nitrogen occurred during the after period. The total calories were 2651 in 24 hours. Röse attributes the negative nitrogen balance on the same nitrogen intake during the main period to the lack of an excess of base. The less the formation of ammonia, the smaller is the wear and tear quota. Thomas had already found earlier that the value for the smallest protein requirement cannot be kept constant with bread and meat, if sufficient basic substances are not simultaneously present. This phenomenon is due to the marked formation of ammonia.

It has already been mentioned that the biological value of individual protein substances differs, that is, the capacity of individual protein substances to attain a minimal nitrogen balance, differs. With milk, Röse achieved this with 20.5 gm. protein; in the case of a potato diet, with 26.5 gm.; with an exclusive banana diet it required 46 gm.

So far as I know, there have never been any studies anywhere which were carried out on a human being who existed for 15 years on an average daily protein intake of 38 to 40 gm.; who during an experimental period lasting for years took daily only 26 gm.; and who at times, during periods of negative balance, took only 20 gm. of protein. Neither Hindhede nor Chittenden, Thomas, Rubner, or Lusk has been able to carry through such series of investigations. The unique character of these experimental conditions led us to report the results of efficiency tests in this subject.

Röse carried out extraordinary performance tests in 1931 together with his friend Dr. Schmitt, a Swiss physician of Thun, who for 25 months likewise ate only about 30 to 40 gm. of vegetable protein with an adequate

caloric intake. Dr. Röse (D. R.), at that time almost 70 years of age, climbed several mountains over 4000 meters in height. Dr. Schmitt (D. Sch.), who at that time was 35 years of age, climbed in 22 ascents, for example, Monte Rosa (4500 m.), the Matterhorn (4500 m.), the Weisshorn, Grosse Viescherhorn and other mountains without disturbance in his efficiency, signs of great fatigue or any indication of exhaustion in spite of the small intake of protein.

Because of its general biological significance, I should like to mention in addition the negative balance experiments which Dr. Röse carried out on himself. We studied him at the end of this period. The total protein intake was 23 gm.; the minimum requirement as determined from the preliminary studies of years, 28 gm. There was no vitamin lack. The amount of calories ingested was adequate. There slowly developed an increasing loss of appetite, diminution of interest in work and a feeling of depression. The experiment had to be interrupted because of these complaints. A second period of equal duration had to be interrupted because the complaints grew intolerable.

The question as to whether during a state of minimal nitrogen equilibrium, the most strenuous bodily exertion results in a greater output of nitrogen, i.e., an increased destruction of protein, in a healthy individual, can be answered in the negative as a result of Röse's studies in Switzerland in connection with his mountain climbing, and our own experiments with the brake ergometer and marching exercises (Marschleistungen). During mountain climbing Röse had a positive balance with 24 to 29 gm. protein in his diet and excellent physical efficiency. In our clinic D. R. showed an average nitrogen output of 3.9 gm. daily. He remained in nitrogen balance. For days at a time he worked at the brake ergometer to the point of exhaustion, without developing a negative balance. Further he walked 50 km. on a hot sunny afternoon in mountainous country without being exhausted or showing an increased nitrogen secretion.

It seemed of interest to us to test the oxygen consumption during and after work. We made the investigation with Krogh's brake ergometer, changing the load and the speed. The same tests were carried out on D. Sch. by Brumann. We were able thus to determine that the oxygen consumption is less per unit of time, but that the period of recovery (corresponding to the oxygen debt) is nevertheless distinctly prolonged. We have made approximately 20 similar tests in the past three years, always with similar results.

In 1933 and 1935 we studied the basal metabolism after a protein poor period and after meat. All the following studies of the respiratory gas exchange were made with the Grafe Universal respiratory apparatus, the gas analyses being carried out with the Haldane Carpenter apparatus.

The values are presented in table 1. The amount of rise was calculated in accordance with the Harris-Benedict tables. The average elevation both

TABLE I

Basal Metabolism Figures

Date	Calories	R.Q.	%
3/13/33	1633	0.81	+16
3/15/33	1636	0.82	+17
1/3/35	1567	0.84	+18
1/4/35	1478	0.82	+11
1/6/35	1489	0.86	+12
1/8/35	1549	0.83	+16

in 1933 and 1935 is about 15 per cent. The values are not comparable with standard figures since D. R. is an unusually energetic, muscular, high spirited man who, from the biological viewpoint, is not as old as would be assumed from his actual age. On each occasion we gave D. R. a careful physical examination. The findings, including roentgen studies, showed no indication of any demonstrable disturbance or wear and tear in his internal organs. There was complete lack of any definite indication of arteriosclerosis. While in the case of D. Sch. the basal metabolism was depressed by about 10 to 15 per cent during the protein poor period of his test, I found a measureable increase in the case of D. R. I prefer not to consider this a true increase in the total combustion but, for the reasons mentioned above, believe these values to represent his normal figures.

The studies of specific dynamic action which, so far as I am aware, have never previously been carried out on a man of this age under similar nutritional conditions, gave peculiar results in 1933. We were interested in the question of the specific dynamic effect of the protein poor diet. The result surprised us in that the increase in total combustion was extraordinarily high and still remained considerably elevated even after six hours. This was confirmed in a control test.

TABLE II

Specific Dynamic Effect after Potatoes (3/14/33)

Time	Calories	R.Q.	%	
1 hour	2204	0.79	+35	350 gm. potatoes, 100 gm. butter, 20 gm. sugar. Total calories 1226.3; P. 8.5 gm., F. 85.8 gm., C. 93.56 gm.
2 hours	1958	0.83	+19	
3 hours	2045	0.88	+25	
4 hours	1810	0.81	+11	
5 hours	2575	0.89	+58	
6 hours	2570	0.89	+57	

The elevation of metabolism was already perceptible after one hour, and after six hours was still 57 per cent. A few days later we then gave a 10-fold greater quantity of protein in the form of meat (table 3). The maximal increase occurred in the first hour and amounted to 22 per cent.

TABLE III

Specific Dynamic Effect after Meat (3/17/33)

Time	Calories	R.Q.	%	
1 hour	1986	0.83	+22	400 gm. meat; 73 gm. butter. Total calories 1194; P. 80.5 gm.
2 hours	1866	0.87	+14	
3 hours	1839	0.71	+13	
4 hours	1940	0.72	+19	
5 hours	1809	0.81	+11	
6 hours	1955	0.82	+20	

After a further three day meat diet we determined the specific dynamic effect again and found a very delayed rise, which began only after four hours. The highest value was attained after 5½ hours amounting to + 26 per cent (table 4).

TABLE IV

Specific Dynamic Effect after Meat (3/20/33)

Immediate	− 0.9%	400 gm. meat; 73 gm. butter. Total calories 1194; Protein 80.5 gm.
½ hour	− 1.3%	
1 hour	+ 0.2%	
1½ hours	− 1.3%	
2 hours	+ 9.0%	
2½ hours	+ 3.5%	
3 hours	+ 6.7%	
3½ hours	+ 2.3%	
4 hours	+16.5%	
4½ hours	+11.1%	
5½ hours	+26.1%	
6 hours	+ 9.4%	
6½ hours	+17.3%	
7 hours	+21.7%	
7½ hours	+17.5%	
8 hours	+19.3%	
8½ hours	+ 6.7%	
9 hours	+ 7.0%	
9½ hours	+10.4%	

After two years of a protein poor diet, conditions were somewhat different. We arranged, instead of a test of short duration, a period of study lasting 24 hours. The apparatus made it possible to study an individual all day and all night and permitted taking food during the same period. On this occasion the total metabolism rose during the afternoon by 37 per cent. It is to be noted that a small percentage of the increase must be attributed to muscular exertion, as D. R. did not lie quietly at rest. During the night the metabolism fell 13 per cent (table 5). After six days we again studied the specific dynamic effect after meat. The increase here was again about the same as before (table 6). To what may now be attributed the altered behavior of the metabolism?

TABLE V

24 Hour Test (1/5/35)

Time	Calories	R.Q.	%	Diet
8:15 a.m.–12:43 p.m.	1838	0.81	+24	8:15 a.m. coffee 400 gm.; cream 20 gm.; sugar 20 gm.
12:48 p.m.– 5:53 p.m.	1875	0.83	+27	12:15 p.m. potato 300 gm.; tomatoes 100 gm.; butter 100 gm.
5:58 p.m.–10:46 p.m.	2020	0.84	+37	3:15 p.m. coffee 400 gm.; cream 20 gm.; sugar 20 gm.
2:52 a.m.– 6:11 a.m.	1282	0.86	−13	
6:18 a.m.– 8:51 a.m.	1489	0.86	+ 1	6:15 p.m. curdled milk 400 gm.; crackers 50 gm.; butter 50 gm.; sugar 30 gm.

TABLE VI

Specific Dynamic Effect after Meat (1/11/35)

Time	Calories	R.Q.	%	
1 hour	1854	0.85	+25	
2 hours	1918	0.79	+30	Meat 400 gm.; butter fat 65 gm. Total calories 1067; P. 88 gm.; F. 77 gm.; C. 3 gm.
3 hours	1838	0.80	+24	
4 hours	1979	0.76	+34	
5 hours	1598	0.83	+ 8	
6 hours	1898	0.86	+28	

No assured interpretation can be given, as long as the nature of specific dynamic action itself is not clear. For the present we must limit ourselves to reporting the observed facts.

During the course of the protein minimum experiment we studied the loss of nitrogen through the skin. We determined the amount of protein given off by means of the skin and perspiration over an experimental period of five days during which unmeasureable losses were avoided so far as possible. The method was the same as that used by Rübner. I give our results, inasmuch as these experiments have only rarely been carried out and since in accurate equilibrium experiments these values must be taken into consideration. During the five day experimental period there were excreted through the skin 0.483 gm. of nitrogen. We studied the blood chemistry in the case of D. R. during the 1935 experimental period both before and after the meat diet. The blood sugar was 89 mg. per cent before the meat diet, and 92 mg. per cent after it was begun. The non-protein nitrogen was normal, 39 mg. per cent; blood chlorides were 514 mg. per cent; blood uric acid 3.32 mg. per cent. Similar values were obtained during both meat and vegetable diets.

From the studies on D. R. it may be concluded that it is possible to live for years on a one-sided diet which includes protein foods of high biologic value such as potatoes and milk, which has an adequate vitamin and caloric

content, and an amount of protein which is extraordinarily small as compared to the general average consumption and by Voit's and Rubner's figures. In spite of this, vigorous physical activity was possible without any demonstrable hurt and without a negative balance during the period of exertion. D. R. puts great faith in potatoes to cover his protein requirement. He has succeeded in cultivating a potato which is unusually rich in protein and palatable, the protein content of which amounts to more than 2 to 3 per cent. It is no doubt possible to live for a long period, without injury to health, on a low protein diet containing approximately 30 gm. of protein. The positive balance is immediately changed to a negative balance if the physiological discharge of vital functions is disturbed by illness. A harmless illness occasions an increased protein consumption under these dietary conditions, thereby bringing about a negative balance. D. R. has often confirmed this. Therefore, a surplus of at least 10 to 15 gm. is necessary for the safety of the organism. But other observations also give rise to the presumption that demands are laid upon the vital reserves by such a nutritional program. Towards the end of the two year series of experiments D. Sch. observed that he experienced an increased need of rest, his pulse became slower and the axillary temperature rose. Süsskind's investigations cannot be subjected to critical study since they were carried out with a protein which was not biologically of high quality, with insufficient vitamin feeding and without accurate analyses. It may be assumed that he lived for a long time in a state of negative balance and that the marked disturbances and resultant collapse are thus to be explained.

If we compare the experiments of Stefansson and Andersen with those of Röse, representing two extremes, we realize how adaptable the human organism is and how multifarious must be its system of safeguards. The meat and fat eaters showed a normal behavior in every respect—total metabolism, protein metabolism, kidney function, efficiency, blood synthesis —in short, all measureable functions except the calcium metabolism were undisturbed. In the case of Röse too all body functions were normal. Physical efficiency was indeed astonishingly good.

Both forms of diet are out of the question so far as actual practical use is concerned. Strong will power and a high degree of fanaticism are necessary in order to follow so one-sided a diet for a long period of time. That it is possible is shown by these investigations.

Summary

Metabolism studies were carried out on a 70 year old, healthy man who for years had been on a diet containing about 30 gm. of protein daily. The basal metabolism was elevated 15 per cent in comparison with the Harris-Benedict figures. The specific dynamic effect of protein was higher after vegetable protein than after meat protein. The blood chemistry was un-

changed. Physical efficiency was excellent. After the most severe bodily labor there was no increased excretion of nitrogen. The nitrogen output through the skin amounted to 0.483 gm. over a five day period.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

A PHARMACOLOGIC STUDY OF THE MECHANISM OF GOUT*

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DR. PRATT's long interest in and contributions to the subject of gout make it a particularly appropriate subject for his birthday volume. It is especially fitting that these observations be reported here since they had their inception in a research the author was privileged to share with Dr. Pratt.[1]

In these experiments we concluded that the action of cinchophen on uric acid excretion was exerted through the central nervous system. At that time methods for testing this suggestion were wanting. With the development of new methods it became possible to test this hypothesis in the experimental animal. In the last three years I have shown that the above concept is correct and that the effects of cinchophen on uric acid excretion do, in fact, depend upon an intact renal nerve supply. This lends support to the idea that the syndrome of gout is associated with changes in the function of the autonomic nervous system, through a mechanism similar to the one concerned in the action of cinchophen on the uric acid excretion.

Thannhauser [2] has long maintained that the mechanism of uric acid retention was primarily a renal dysfunction, probably concerned with the nervous connections of the kidney. While the frequent association of nephropathy with gout has been adequately stressed, the numbers of patients without evidence of renal lesions have militated against the whole-hearted acceptance of the renal theory.[3] Thannhauser based his idea of the effects of the renal nervous mechanism on the experiments of Ellinger and Hirt.[4] These experiments, however, showed relatively small differences and were acute experiments with all the difficulties and extraneous factors that acute experiments under anesthesia entail. Although the variations in excretion that they report seem very small, they evidently felt them to be sufficiently constant and consistent to draw the conclusion that the renal nerve supply affected renal cellular activity and that these nerves, therefore, were "secretory nerves" in addition to being "vasomotor nerves." Marshall and Kolls [5] working with anesthetised dogs were unable to confirm their results and concluded that these nerves had only a vasomotor function.

In 1931, Pratt and I [1] concluded that the action of cinchophen on uric acid excretion was through the central nervous system. This conclusion was arrived at by a study of the uric acid excretion of normal human individuals and a consideration of the literature. Since that time studies on

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the action of cinchophen have concerned themselves primarily with the toxic effect on the liver and have not thrown any new light on the mechanism of its action on the uric acid excretion. Since the end product of nucleic acid metabolism in the dog is chiefly allantoin with only small amounts of uric acid, it was only with the introduction of a rapid, accurate colorimetric method for the determination of allantoin [6] that it became possible to undertake a series of crucial experiments as to whether the above-mentioned hypothesis concerning the action of cinchophen was correct. In brief, if cinchophen acted on the end-product of nucleic acid metabolism as a part of its action on the central nervous system, it would be a simple matter to prove or disprove this point by giving the drug to animals whose kidneys had been disconnected from the central nervous system. Such experiments were undertaken. Fortunately the study of the uric acid excretion was made in addition to the allantoin excretion. It was found that the effect of cinchophen on the uric acid excretion was profoundly modified by denervation of the kidneys whereas the effect on allantoin excretion was only slightly changed.[7] When cinchophen is given to the dog an increase in allantoin and uric acid excretion occurs without an increase in urinary volume. This seems to support Thannhauser's idea that the drug acts chiefly by increasing the concentration of uric acid in the urine. When, however, the drug is given to a dog with denervated kidneys, instead of causing an increase in uric acid excretion, a decrease occurs despite the fact that the volume of urine is always greater in the dog with denervated kidneys.[8] It is evident from this that the action of cinchophen is not primarily concerned with concentration. Since the uric acid in the urine of a normal dog may be entirely exogenous, it seemed desirable to try the effects of the drug on a Dalmation hound which as a constitutional anomaly is unable to oxidize all uric acid into allantoin, occupying a position in this respect midway between other dogs and man. A chart of one of our experiments on a pure-bred Dalmation dog is shown herewith (figure 1). It will be seen that the effect of cinchophen on the excretion of uric acid is reversed as is the case in the normal dog. This reversal becomes progressively less as time goes on, and as regeneration of the renal nerves is completed the original reaction is restored. This experiment disposes effectively of the contention that there may be a difference in the handling of exogenous and endogenous uric acid, at least as far as the kidney is concerned. While these experiments show conclusively that the action of cinchophen on uric acid excretion is mediated through the nervous system, the increase in allantoin excretion was not explained. In order to understand this mechanism better it was decided to try to separate the sympathetic from the parasympathetic supply of the kidney by pharmacological means since this cannot be done satisfactorily by surgical methods.

To accomplish this two drugs are available. Ergotamine and atropine in adequate doses will block sympathetic and parasympathetic impulses re-

spectively. It must be remembered that the latter connections of the kidney are partly through the celiac ganglion though some direct connections have been described.[4, 9] It seems likely from Feldberg's work,[10] that preganglionic fibers are cholinergic and may be affected by atropine even though the impulses they carry terminate in so-called adrenergic postganglionic fibers. Consequently, complete separation of the two parts of the sympathetic system is not possible and overlapping of results may occur. However, by

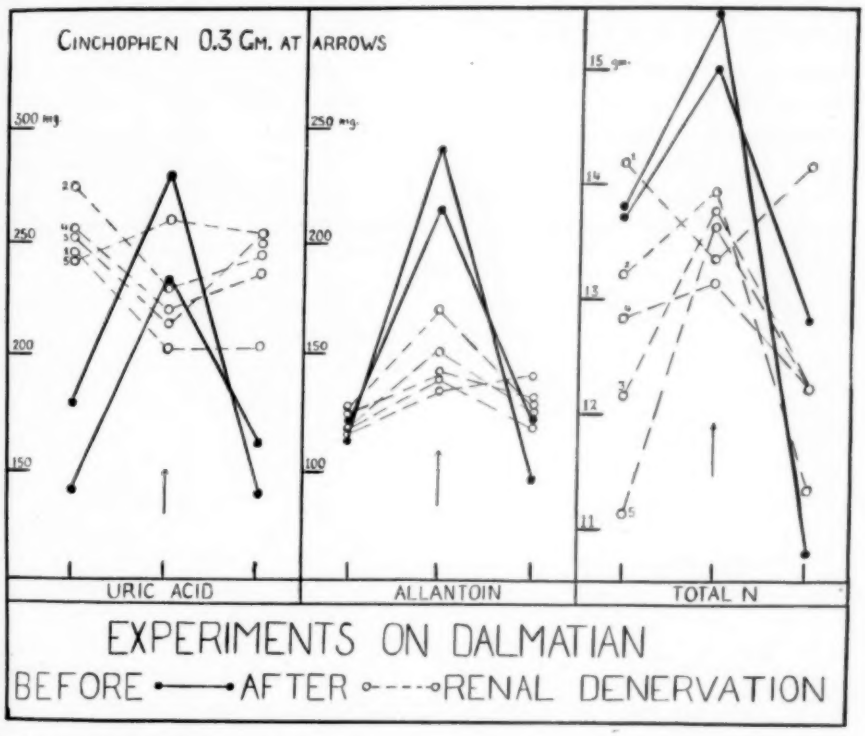

FIG. 1. Each point on abscissa represents the average 24 hour excretion of a three day period. The figures opposite the dotted line curves indicate the order of the experiments after the kidneys had been surgically denervated.

pharmacologic means plus the application of anatomic facts, the two systems can usually be separated by inference at least.

The results of experiments [11] employing either ergotamine or atropine simultaneously with cinchophen are compared with the effects of complete renal denervation in the accompanying table. A consideration of these results indicates that the effect of cinchophen on allantoin excretion is mediated through the parasympathetic whereas that on uric acid excretion is mediated by the true sympathetic. It becomes clear from this that uric acid excretion may be modified by the autonomic nervous system.

If this be true, ergotamine in appropriate doses might affect uric acid excretion under certain conditions. In the experiments cited above ergotamine alone had no significant effect on either uric acid or allantoin excretion but did produce a diuresis. The same dose was able to modify the effect of cinchophen on uric acid excretion. Its action therefore is such that it may modify abnormal stimuli to uric acid excretion through the sympathetic. Any effect on uric acid excretion after the exhibition of this drug suggests the existence of abnormal sympathetic impulses through the renal nerves. This possibility had been foreseen many years ago by Thannhauser, and Harpuder [12] concluded that there was some diminution in uric acid excretion in normal individuals after the exhibition of ergotamine. However, his figures do not show highly significant changes. In a personal communication, Thannhauser has stated that he has always seen a diminu-

TABLE I

A summary of results obtained in the experimental studies of the uricosuric effects of cinchophen. In each case the comment indicates the results on this action when the indicated drug was given simultaneously with cinchophen.

Action of Cinchophen		
Modified by:	On Excretion of:	
	Uric Acid	Allantoin
Denervation of kidney	Reversed	0
Atropine	0	Eliminated
Ergotamine	Eliminated	Eliminated

tion in uric acid excretion produced by the administration of ergotamine to gouty individuals and even the precipitation of an attack of gout. Hench,[13] too, has mentioned two similar observations.

We have had a brief opportunity of studying one patient with pure gout under imperfect metabolic conditions. However, this patient is crucial in that careful investigation had revealed no other disease nor any involvement of the kidneys as such. The accompanying table shows the effect of a single injection of ergotamine on uric acid excretion in this patient. It seems significant that six or seven hours after the injection of the drug, reddening of and pain in the great toe occurred which the patient stated was precisely like his previous attacks which had occurred at sufficiently infrequent intervals to make the single observation of greater significance. The important result of the metabolic study is the diuresis produced by ergotamine with a smaller percentage increase in uric acid excretion. It is to be noted that in the four corresponding periods the creatinine excretion was in each period the same on the control day as on the experimental day, indicating in all

probability that the glomerular filtrate was of the same volume and that the differences produced by the injections of the drug concern reabsorption. Despite the absolute increase in uric acid excretion the concentration was diminished by ergotamine, indicating that the dose used was adequate to have an opposing effect to that of cinchophen. These facts might indicate that the gouty attack and uric acid excretion as such do not necessarily run hand in hand but none the less they are both connected with the autonomic mechanism which controls the concentration of uric acid in the urine. The effect of ergotamine on this gouty individual suggests that some impulses not normally present are acting on the uric acid excreting mechanism in this patient through the renal nerves, and that such impulses are capable of

TABLE II

Twelve hour excretion of J. B. S. as affected by ergotamine. Identity of creatinine figures indicate similar volume of glomerular filtrate. Note the low concentration of uric acid accompanying the mild attack of gout. The blood uric acid remained unchanged, three samples in the first four hours ranging between 4.1 and 4.4 mg. per 100 c.c.

Period Number	Time	Control Day			Ergotamine 1 mg. s. c. at 8 a.m.		
		April 9, 1937			April 7, 1937		
		Volume c.c.	Uric Acid mg.	Creatinine mg.	Volume c.c.	Uric Acid mg.	Creatinine mg.
1	7 a.m.–1 p.m.	252	70	345	705	114	367
2	1–3 p.m.	220	45	160	300	37	130
3	3–5 p.m.	120	35	120	150	38	120
4	5–7 p.m.	220	40	144	175	40	159
Total		812	190	769	1330	229	776

modification by ergotamine in a similar fashion to its action on the stimulus provided by cinchophen.

If gout be a true functional disease of the autonomic nervous system, we should be able to discover in its symptomatology certain other features indicating such a disturbance. The diuresis of the gouty attack has been frequently observed. However, such patients have not been studied otherwise in relation to possible sympathetic disturbances. In the records of the Brigham Hospital, we have found 23 cases of gout without evidence of nephritis and these showed an average daily urinary volume of 1375 c.c., as compared with 850 c.c. in random patients with nonmetabolic diseases in the hospital at the same time, indicating a continuing disturbance of the mechanism of water excretion. Since these cases were not studied at the time with this in mind, other clinical studies relating to the autonomic system are not available. Talbott, Jacobson and Oberg [14] studied two patients and point out that a diuresis occurs before an attack of gout; however, their

tables show a continuing large urinary volume. It has been assumed that the diuresis of gout was an attempt to get rid of uric acid which the gouty kidney was unable to concentrate. However, it has been shown that the gouty kidney can concentrate uric acid as well as the normal.[15] Brugsch[16] has emphasized the importance of the autonomic medullary centers in the control of purin metabolism.

The data collected here suggest that the etiology of gout may well be sought in functional disturbances of the vegetative nervous system involving especially the innervation of the kidney.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

LYMPHOSARCOMA CELL LEUKEMIA *

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IT has been observed frequently that the blood of patients with lymphosarcoma may become leukemic. This syndrome has been characterized as leukosarcoma by Sternberg [1] or as lymphosarcoma terminating in lymphatic leukemia.[2, 3, 4] Flashman and Leopold [5] noted 107 cases of this type in the literature and described an additional case. On the basis of a lymphosarcoma presumably terminating in lymphatic leukemia, numerous speculations have been published concerning the relationship of these two conditions. A careful cytological study of the cell types in this form of leukemia has shown, however, that the cells are not lymphocytes, but lymphosarcoma cells, so that the condition is a true lymphosarcoma cell leukemia.

MATERIAL AND METHODS

Of 43 patients with known lymphosarcoma, 15 developed a leukocytosis during the course of the disease. This group comprised 10 males and five females. There were eight positive biopsies and six autopsies. The ages of the patients ranged from six to 70 years, with a fairly even distribution in the intervening decades, except that between 21 and 30 years, which included one third of the patients. Warthin [6] noted leukemic transformation in nine cases of lymphosarcoma, out of a group of 134 biopsies.

To note how a lymphosarcoma cell would appear if it was in the blood stream, pieces of fresh lymphosarcoma glands were stirred in blood serum, and films were made of this suspension. These were stained with Wright's stain alone or preceded by brilliant cresyl blue while the cells were in the moist state.

THE LYMPHOSARCOMA CELL

The lymphosarcoma cell in the blood stream is usually mistaken for a lymphocyte. There are certain differentiating features, however, the most marked being the peculiar characteristics of the nucleolus. This is usually eccentrically placed, single, very rarely multiple. In the films made on brilliant cresyl blue containing cover glasses, later stained with Wright's stain, the nucleolus stands out as a sky blue, round area, surrounded by a deep, blue black rim of chromatin which is piled up around it. (Figure 1.) In the true immature lymphocyte or lymphoblast, under these conditions, the

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nucleolus appears as a light blue " hole " or area in the chromatin structure, without the heavily staining rim. The nucleoli are more likely to be multiple in the immature lymphocytes or lymphoblasts than in the lymphosarcoma cell.

The lymphosarcoma cell, in films, varies in size from 7.5 by 9 microns to 12 by 13.5 microns. The nucleus is usually oval or oblong, occasionally being egg shaped (thicker at one end) in films. Kidney shaped or notched forms are common in some specimens. The stained chromatin is coarsely reticular and somewhat spongy in structure and the chromatin around the edge is thickened into a fairly definite nuclear wall, differing in this respect from the monocyte. The cytoplasm of the cell is sparse, deeply basophilic, and with the brilliant cresyl blue, Wright's stain, appears as a fine, blue lacework.

In sections of fixed tissue, the lymphosarcoma cell is large and round, resembling the lymphoblast in size and proportion of practically non-granu-

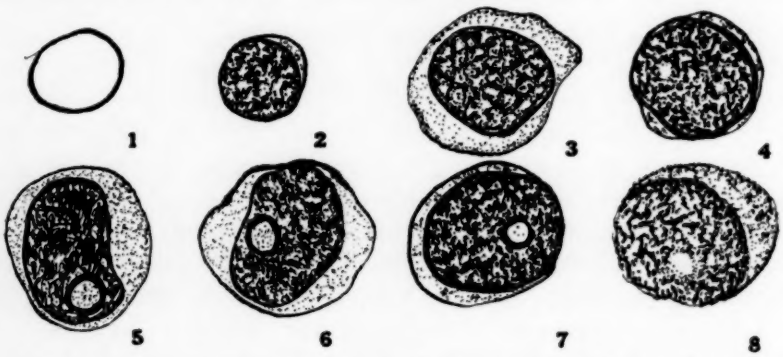

FIG. 1. Cells from peripheral circulation. Stained supravitally with brilliant cresyl blue and counterstained with Wright's stain. (Camera lucida drawings) 1–4 normal blood. 1. Normal red blood cell, for size comparison. 2. Small lymphocyte. 3. Large lymphocyte. 4. Large immature lymphocyte, with several small nucleoli. 5, 6, 7. Cells from lymphosarcoma cell leukemia. 8. Lymphocyte from lymphatic leukemia.

lar cytoplasm. The nucleus may be irregular in size and shape, many showing indentations on lobulation.

These cells were studied supravitally by Wiseman [7] who found that unlike mature lymphocytes, they did not show motility, although both types did not show evidence of phagocytosis. The mitochondria were described as dust-like, as compared to the large rods and spheres of the mature lymphocyte and the small spheres of the lymphatic leukemia cell. Deep scarlet neutral-red vacuoles, 1 to 10, were present at the periphery of the nucleus in the " sarcoma cell " although they were absent in the leukemic cell and, when present in the mature lymphocyte, they stained rose red.

THE BLOOD

There appear to be two phases of the blood in patients with lymphosarcoma—an aleukemic and a leukemic phase. In the aleukemic phase, the

leukocyte count varies from 6,000 to 10,000 per cubic millimeter with 30 to 40 per cent "lymphocytes." Many of these cells are not lymphocytes, but lymphosarcoma cells. The percentage varies from 3 or 4 to 25 or 30 in this group. In the leukemic phase, the count rapidly increases to an average of 70,000 $\pm$ 43,200 per cubic millimeter, the highest count in this series being 156,000 per cubic millimeter. As the count increases, the bulk of the cells are lymphosarcoma cells, which in some cases form 98 per cent of the total.

As the leukemic process progresses, anemia becomes more marked, the average red blood cell count being around 2.5 million per cu. mm. In some patients it reached a much lower level (0.8 to 1.0 million). The color index was most frequently around 1 or slightly below. The blood platelets were increased in number in the early stages, but decreased in the late stages.

Clinical Course

In most of the patients, enlargement of lymph nodes was the first sign noted. Visible tumors in the neck region were the first evidence in three patients; inguinal nodes in two; mediastinal (cough, dyspnea, pleural effusion) in three; abdominal symptoms in two; sore throat in four; weakness in two and submaxillary enlargement in one. Symptoms, in order of their frequency, were weight loss (average 15 pounds); fever; bleeding (petechiae, hemoptysis, hematuria, epistaxis, hematemesis, gross bleeding from mucous membranes, retinal hemorrhages); joint pains; pulmonary and hilar lesions (roentgen-ray changes, pleural effusion, dyspnea, chest pain, cough); allergic symptoms; herpes; skin lesions (toxic erythema, erythema multiforme); bone lesions; facial palsy; diplopia; local edema. Albuminuria (trace), during some stage of the disease was common. The spleen size varied from 15 to 23 centimeters (average 16.5 cm.); and at autopsy the weights varied from 490 to 700 grams. The spleen was palpable in seven patients.

With the onset of the leukemic phase, fever was common (100 to 105° F.). Terminally, 104° to 107° F. were noted. Lung involvement was not always definitely indicated on the roentgen-ray plates, although autopsy in some of these patients showed infiltration of the alveolar walls and of the perivascular and peribronchial tissue with lymphosarcoma cells. This type of lesion was most common in patients dying in the leukemic state, whereas in two who were aleukemic on the day of death, the lungs were not involved. The degree of leukemia was more parallel to the lung involvement than to the degree of peripheral lymph node enlargement.

The duration of the disease varied from 2.5 to 36 + months. The duration of the leukemic phase varied from two days to 60 days in eleven patients in whom approximate data were available. One patient, however, gave a history of a leukemic blood picture (94,000 per cu. mm.), diagnosed as lymphatic leukemia, for over seven years. This patient had a white

blood cell count of 37,000 when first observed at this clinic, with 84 per cent lymphosarcoma cells. He died 27 days later. The maximum count was 73,000. The average duration of the leukemic phase in all of the other patients was 26 days.

Nine patients gave a history of one or more of the common childhood diseases. Of the others, three gave a history of a symptom complex which they were told was influenza.

Lymphosarcoma and Pregnancy

One patient with lymphosarcoma showed a remission during a period of pregnancy. The patient, a 31-year-old woman, was first studied after she had had cervical and axillary glandular enlargement for 18 months. Her blood count at that time was as follows: Red blood cell count 3,500,000 per cu. mm.; white blood cell count 47,800; hemoglobin 67 per cent (Sahli), 9.38 grams per cent; atypical "lymphocytes" 65 per cent; blasts 0.5 per cent. She became pregnant six months later, and during the third month she returned to the clinic for examination. At that time her red blood cell count was 4 million per cu. mm., white blood cells 7,100 per cu. mm., hemoglobin, 12.93 grams per cent, polymorphonuclear neutrophiles 71 per cent, large lymphocytes 15 per cent, small lymphocytes 9 per cent, monocytes 5 per cent. The adenopathy had practically disappeared. A perfectly normal child was born in due course of time, and eight months after this the blood count was still normal, but lymphosarcoma cells were noted on the blood films. About nine months after this, the patient returned in complete relapse, with a red blood cell count of 800,000 per cu. mm., white blood cells 4,200, hemoglobin 2.88 grams per cent. Lymphosarcoma cells, 27 per cent, and one blast were noted. She received two blood transfusions and had another remission. An examination four months later showed her red blood cells at a level of 3,600,000 per cu. mm., white blood cells 6,100 and hemoglobin 75 per cent (Sahli) (10.5 grams per cent), "lymphocytes" 59 per cent.

Effect of Roentgen-Ray Irradiation

In 11 of the patients the leukemic phase started after roentgen-ray therapy, in two no roentgen therapy was given, and in two it is uncertain whether the patients had received roentgen therapy before they reported to the hospital or not. A decrease in the number of leukocytes followed roentgen-ray therapy during the leukemic phase, in 8 patients, with severe leukopenia (3,500, 1,800 and 350 per cu. mm.) developing in three patients. In five patients there was a subsequent increase in number after the initial decrease. There appeared to be two stages in the effect of roentgen-ray therapy, an initial decrease in the number of leukocytes, followed by a marked and rapid increase. Thus in one man with a leukocyte count of 50,000 per cu. mm. (96 per cent lymphosarcoma cells), 2800 r were given over 12 positions from May 20 to June 4. On the last day the count was

33,000 per cu. mm. Two days later the count was 156,000 per cu. mm. and the patient died. In another patient the initial count was 10,500 leukocytes per cu. mm. On five successive days, 150 r were given. The leukocyte count fell to 5,500 per cu. mm. It then rose gradually to 15,200 with 66 per cent lymphosarcoma cells 43 days later. Three days before death, which followed in two weeks, the count was 92,000, with 85 per cent lymphosarcoma cells. A third example is that of a patient with 7,800 leukocytes per cu. mm., who received 1,200 r over a five day period. At the close of the treatments the leukocyte count was 6,800 per cu. mm. An observation 41 days later showed that the count had increased to 50,000 per cu. mm. and three days later to 70,800 per cu. mm. The patient died within four weeks.

Pathological Changes in the Organs

Autopsy studies of the organs of patients dying during the leukemic phase showed transformation, in varying degrees, of all lymphoid tissue in the body, into the lymphosarcoma type. The lymphoid follicles of the intestine and colon, as well as the tonsil showed this change. There was marked invasion of the bone marrow and subperiosteal extension, which also involved the surrounding tissues. All of the organs showed invasion with lymphosarcoma cells. Among those showing perivascular or tissue infiltration were the brain, capsule of the pituitary, the fatty envelope of all the organs (heart, kidneys, aorta), the myocardium, beneath the epicardium, bronchi, pulmonary alveolar walls, thyroid, esophagus, thymus, spleen, diaphragm, stomach, liver, gall-bladder, adrenal, kidney, ureter, skin, testes, epididymis, seminal vesicles and vas deferens. The skull, when involved, showed osteolytic lymphosarcomatous infiltration.

Discussion

The frequent occurrence of the leukemic state of lymphosarcoma after roentgen-ray therapy is of interest in connection with the observations of Krebs, Rask-Nielsen and Wagner [8] on the production of a "leukosarcomatosis" (aleukemic and leukemic) in white mice after irradiation. They found that the leukemic phase developed late in the course of the disease, and that, as in the cases cited here, the prognosis was bad.

In view of the tendency of the lymphosarcoma cell to invade the tissues, it is not surprising that some of the cells enter the blood stream. However, it appears that the number does not reach leukemic proportions until there is extensive growth in moving organs, as the lungs. This phenomenon is similar to that found in other types of leukemia (Isaacs [9]).

Summary and Conclusions

1. The characteristics of 15 cases of lymphosarcoma cell leukemia are given.

2. The lymphosarcoma cell has characteristic cytologic features which facilitate its recognition in the blood stream. This cell type may constitute 4 to 98 per cent of the leukocytes in the peripheral circulation.

3. The leukemic phase is usually ushered in with exacerbation of symptoms and fever.

4. The leukocyte count may reach a maximum of from 23,000 to 156,000, and there is progressive anemia and thrombocytopenia.

5. The duration of the leukemic phase varies from two to 60 days (average 26 days) although one patient had a history of leukemia for over seven years.

6. There may be relapses and remissions, but the prognosis is poor. A temporary remission may be induced by roentgen-ray therapy, but this is followed by a relapse and death.

7. The disease appears to be a true lymphosarcoma cell leukemia, rather than lymphosarcoma turning into lymphatic leukemia.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

THE FLOW AND CONCENTRATION OF BLOOD AS INFLUENCED BY ERGOT ALKALOIDS AND AS INFLUENCING MIGRAINE *

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IN about 90 per cent of patients suffering from an attack of migraine headache, the injection of ergotamine tartrate causes complete disappearance of the pain and other symptoms.[1] In the case of the more recently isolated alkaloid of ergot, ergonovine, clinical results are not so striking. In our 54 patients who received injection of the drug, pain was stopped in 39 per cent and was improved in a further 40 per cent.[2] The beneficial action of ergot seems to be specific for headaches of the migraine type.[3] These welcome therapeutic results led us to investigate the physiological effects of these ergot derivatives.

In this communication we report the action of ergotamine and of ergonovine on the speed of flow and on the concentration of blood as revealed by measurement of blood gases. No observations of blood flow have been reported for ergonovine. As for ergotamine tartrate, Lennox, Gibbs and Gibbs,[4] by means of a thermoelectric flow recorder inserted in an internal jugular vein of migraine patients, obtained records showing an increase of cerebral blood flow after intravenous injection, presumably a result of the coincident increase in blood pressure. On the other hand, Herrick,[5] in dogs, obtained large increases in blood pressure but a decrease in blood flow which, on the average, was only one-fourth its initial value. Presumably, the difference in results can be accounted for by the fact that his dogs received a dose three or four times that used by us in human subjects.

Because epinephrine has been considered pharmacologically as the antagonist of ergotamine, parallel observations were made with this drug.

MATERIALS AND METHODS

Epileptic and other patients on the Neurological Service at the Boston City Hospital were used for these observations. Subjects were in bed but not fasting. Blood was drawn from the arm without stasis under oil, chilled and analyzed at once in the apparatus and by the technic of Van Slyke.[6] After the preliminary blood sample was taken, the subject was given either ergotamine tartrate, 0.5 mg. intravenously; or ergonovine, 0.6

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mg. intravenously or 12 c.c. by mouth; or epinephrine, 0.1 mg. subcutaneously.* Records were kept of the subject's blood pressure and pulse rate and of his symptoms. The second blood sample was taken after a lapse of from 30 to 60 minutes (the interval required for ergotamine to stop a headache). After epinephrine injection, the interval was 40 to 70 minutes, the effort being to secure blood while the reaction was at its height.

Ordinarily, an alteration in blood flow would be shown by an alteration of oxygen content, but when the concentration of red cells is changing, measurement of the oxygen saturation also is necessary. The percentage of saturation was obtained by dividing the oxygen content of the blood by its oxygen capacity. Changes in the oxygen capacity of the blood represent changes in the concentration of the red cells. Results will first be stated, then discussed.

Effect on Oxygen Saturation of Venous Blood

Ergotamine Tartrate. Fourteen observations were made of changes in the blood gases of the venous blood of the arm following the intravenous injection of ergotamine. In all these observations there was a wide scattering of individual results, but nearly all were in the same direction. After injection of ergotamine, in three instances there was a decrease of oxygen saturation and in 11 an increase. The average change was an increase of 8.1 per cent (i.e., from an oxygen saturation before injection of 63.5 per cent to 71.6 per cent saturation after injection). (See the accompanying table.) The percentage increase in the average oxygen saturation of the blood (12.7 per cent) was not as great as the percentage increase in its oxygen content (17.7 per cent), because the oxygen capacity of the blood also increased.

Ergonovine. Eighteen patients were given ergonovine (*Ergoklonin*). In six instances, administration was intravenous, and in 12 instances, by mouth. The average oxygen saturation of venous blood showed a definite increase of 10.6 per cent when the drug was injected and of 4.2 per cent when it was ingested. A change greater after intravenous injection than after ingestion was to be expected. The greater effect of ergonovine than of ergotamine is explainable by the larger dose contained in an ampule of ergonovine.

Epinephrine. This drug was injected in 13 instances. Results were less uniform than in the case of ergot. A decrease in the oxygen saturation

* Ergotamine tartrate (*Gynergen*) was supplied by the Sandoz Chemical Works, Inc., of New York, and ergonovine (*Ergoklonin*), by John Wyeth and Brother, Inc., of New York. Each of these firms also contributed funds for the research. Ergonovine was so named by the Council on Pharmacy and Chemistry of the American Medical Association. *Ergoklonin* is a trade name. The preparations of *Ergoklonin* furnished us, being brownish in color, presumably contained ingredients other than ergonovine, which in solution is clear. *Ergoklonin*, however, had an action similar to other preparations of ergonovine in the clinical and laboratory tests which we used; 0.2 to 0.3 mg. of ergonovine is equivalent to about 0.5 mg. of ergotamine.

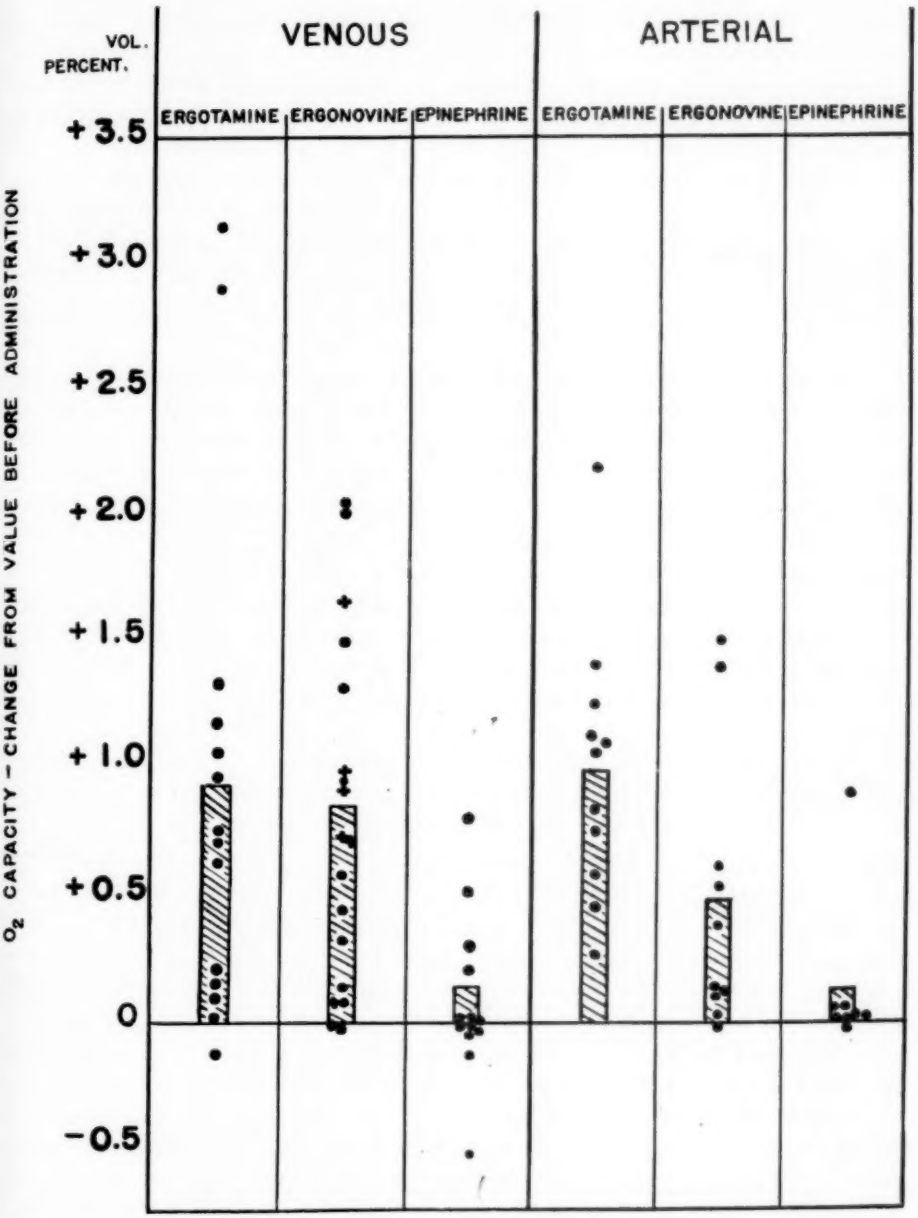

FIG. 1. The average and individual measurements of the change in the oxygen capacity of venous and arterial blood following the administration of ergotamine tartrate, ergonovine (*Ergoklonin*), and epinephrine. The ordinant represents the absolute change in the oxygen capacity in volume per cent. The columns indicate the average measurements for the group, and the dots, the individual measurements. The ergotamine was given intravenously in all cases. The *Ergoklonin* was given by mouth except for those experiments in the venous column which were marked by crosses. Crosses in this compartment indicate medicine given intravenously. The epinephrine in all cases was given subcutaneously.

occurred in four of the 13 observations and the average change was an increase of 5.8 per cent.

Discussion. In résumé, the increase in the average absolute per cent saturation of venous blood for the various groups, as well as the percentage increase over the preliminary measurements was as follows:

			Absolute Increase Per cent	Percentage Increase
Ergotamine tartrate	I.V.	14 cases	8.1	12.7
Ergonovine	I.V.	6 cases	10.6	18.6
Ergonovine	P.O.	12 cases	4.2	8.0
Epinephrine	S.C.	13 cases	5.8	8.9

An increase in the oxygen saturation of venous blood means either a decrease in the consumption of oxygen on the part of the tissues through which the blood passes or an increase in the rapidity with which the blood flows through the part. Epinephrine increases oxygen consumption, whereas in normal persons, ergotamine does not.[7] However, most subjects were more restless after injections than before, and their metabolic rates were presumably increased, therefore the increase in the speed of blood flow through the arms, especially in the case of epinephrine, was probably greater than the measurements indicate. An increased cerebral blood flow following injection of epinephrine [8] and of ergotamine [4] has been demonstrated by other methods. The increased cardiac output from epinephrine is well known.

Effect on Oxygen Saturation of Arterial Blood. Thirty-one observations were made of arterial blood before and after the injection or ingestion of these three drugs. As would be anticipated, changes in the average oxygen saturation were negligible. Ergonovine given by mouth and epinephrine injections caused no significant alterations. After injection of ergotamine, the oxygen saturation decreased by 2.2 per cent. This decrease did not, of course, indicate a decrease of blood flow, the blood being arterial, but was due to an increase in the oxygen capacity of the blood. The oxygen content of the blood did not keep pace with the increase in its capacity, due possibly to an increased speed of blood flow through the capillaries of the lungs which allowed less time for the transfer of oxygen to the blood.

Effect on Oxygen Capacity of Venous Blood. After injection of ergotamine, the oxygen capacity of venous blood was increased in all experiments save one. The average increase was 0.90 volumes per cent (from 19.46 volumes per cent before, to 20.40 volumes per cent after the injection). Increase of a comparable magnitude occurred after ergonovine (0.84 volumes per cent when given intravenously and 0.86 volumes per cent when given by mouth). The changes after injection of epinephrine were variable and the average increase was only 0.15 volumes per cent. Average results appear in the table and both average and individual results are indicated in the figure.

Effect on Oxygen Capacity of Arterial Blood. The average increase in the oxygen capacity after ergotamine injection was 0.98 volumes per cent, and after epinephrine injection, 0.11 volumes per cent. After ergonovine taken by mouth, the average increase was 0.47 per cent which was less than the increase which occurred in venous blood. The average changes in arterial blood after ergotamine and epinephrine were almost identical with those occurring in venous blood.

Consolidating the observations for venous and for arterial bloods, the oxygen capacity of blood was increased by these drugs on the average as follows:

			In Vol. Per cent	Percentage Increase
Ergotamine	I.V.	27 cases	0.94	4.8
Ergonovine	I.V.	6 cases	0.84	4.4
Ergonovine	P.O.	22 cases	0.68	3.5
Epinephrine	S.C.	21 cases	0.13	0.6

Quantitative results therefore differ, the increase being of a different order for ergot derivatives than for epinephrine.

Edmunds and Nelson [9] have reported that the subcutaneous injection of epinephrine in 10 dogs caused an average increase of 23 per cent in the number of red cells of capillary blood. The relatively small change which we observed is probably due to the fact that they injected 50 to 70 times the amount of epinephrine we used. They attribute the polycythemia both to a loss of blood plasma and to the addition of red cells swept from the bone marrow. We have no direct evidence as to which of these changes was responsible for the increased concentration of arterial and venous blood which follows the administration of ergot derivatives.

Inspection of the table shows that, irrespective of changes in the average oxygen content of the blood, the average carbon dioxide content decreased in each of the four different experimental procedures. We believe this decrease was due to increased pulmonary ventilation associated with the restlessness which followed the injection of the drugs.

Discussion. We have observed then that the ergot derivatives, ergotamine tartrate and ergonovine, cause moderate increase in the speed with which blood flows through the arm as measured by the oxygen saturation of the venous blood. This increase presumably is due to the increase in blood pressure which occurred in these cases.[2] The increased pressure presumably followed a mild constriction of peripheral arteries. Pool and Nason [10] observed constriction of dural and skin vessels in animals. In order to account for increased blood flow, the peripheral vasoconstriction, if generalized, must be more than counterbalanced by the cardiac output. The beneficial results of ergot cannot be attributed solely to the increased blood flow, because similar increase in flow took place when adrenalin was injected, but only in a minority of cases is the use of adrenalin followed by relief of migraine headache.

There was an increase in the concentration of the blood following the administration of ergot. The average degree of concentration differed for the three drugs used, the order being ergotamine, ergonovine and epinephrine. This is the same order in which these drugs are effective in stopping migraine attacks. In fact, the quantitative differences between the ergot fractions on the one hand and epinephrine on the other are so great as regards their effect on headache and on the concentration of blood that alterations of blood concentration might be suspected of playing a dominant rôle in migraine headache. We do not believe, however, that relief of migraine attacks is due simply to a concentration of red cells in the blood. If it were, therapeutic results in migraine would have been reported in conditions associated with dehydration of the blood, such as starvation, purgation and profuse sweating.

There is indication, rather, that ergot in the therapeutic doses employed, causes a "tightening up" of the blood vascular system; an increased tone to arteries whose tone may have been impaired, increase in blood flow and possibly of cardiac output, and a decreased volume along with an increased viscosity of the blood. These observations would seem to dovetail with those of Wolf,[11] who, after ergotamine injection, observed a 50 per cent reduction in the pulsation of temporal arteries of patients having migraine headache, the reduction paralleling in time the relief from headache. The increase of spinal fluid pressure which follows injection of ergot, reported by Pool, von Storch and Lennox,[12] might be due to a transfer of fluid from cerebral capillaries. Also, Pool and Nason [10] observed consistent constriction of dural and skin vessels after ergotamine, whereas pial vessels behaved variably. The dural vessels are presumably more at fault in migraine headaches than those in the cerebrum. Our observations, therefore, may form a link in the explanation of the mechanism of migraine headaches when such explanation is complete. The final chain of reasoning must, however, be distinctive for migraine as contrasted with non-migraine headaches, and must explain not only the headache, but the visual, the sympathetic and the peripheral sensory disturbances which form a portion of the migraine syndrome.

Summary

Ergotamine tartrate was administered to 27 subjects, ergonovine to 28 and epinephrine to 21, in order to observe the effect on the flow and the concentration of blood as measured by changes in the concentration of blood gases.

The parenteral administration of ergotamine, of ergonovine and of epinephrine produced a percentage increase in the average oxygen saturation of venous blood from the arm of 12.7 per cent, 18.6 per cent and 8.9 per cent respectively.

The ergot derivatives injected intravenously produced a definite increase in the oxygen capacity of both venous and arterial blood, the combined percentage increase being: for ergotamine, 4.8 per cent, and for ergonovine, 4.4 per cent. In contrast, epinephrine caused insignificant increase, 0.6 per cent.

Therefore, these ergot derivatives, like epinephrine, cause increase in the rate of blood flow through the peripheral tissues. Unlike adrenalin, ergotamine and ergonovine concentrate the blood. The specific effect of ergotamine and of the less effective ergonovine in relieving migraine headache may be partially explained by their action in increasing the tone of arteries. Increase in blood pressure and blood flow and decrease in blood volume may be the result of the increase in arterial tone. These observations may form a link in the chain of reasoning which ultimately will explain the mechanism of migraine.

Effect of Ergotamine Tartrate, of Ergonovine, and of Epinephrine on Blood Gases

Arm Vein	No. of Cases	O_2 Content Vol. %	O_2 Capacity Vol. %	O_2 % Saturation	CO_2 Content Vol. %
Ergotamine, I. V.					
Before	14	12.38	19.46	63.5	53.36
After		14.58	20.40	71.6	51.46
Ergonovine, I. V.					
Before	6	10.76	19.09	57.0	56.23
After		13.50	19.93	67.6	51.48
Ergonovine, P. O.					
Before	12	9.72	18.91	52.1	56.03
After		11.26	19.77	56.3	54.54
Epinephrine, S. C.					
Before	13	13.06	20.26	64.5	52.71
After		14.28	20.41	70.3	47.12
Arterial					
Ergotamine, I. V.					
Before	13	18.61	19.54	95.7	47.97
After		19.18	20.52	93.5	46.88
Ergonovine, P. O.					
Before	10	19.00	20.30	93.5	46.55
After		19.49	20.77	93.9	46.37
Epinephrine, S. C.					
Before	8	19.09	20.24	94.1	48.15
After		18.96	20.35	93.2	47.77

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

INTRAVENOUS LIVER EXTRACT IN THE THERAPY OF PERNICIOUS ANEMIA; REPORT OF A CASE*

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IT is a common observation that patients with pernicious anemia may fail to respond to the oral administration of liver, liver extract and ventriculin, and that these same patients will respond promptly to an extract given intramuscularly. Satisfactory and more rapid improvement in the patient's blood has been frequently noted after intravenous injection of specially prepared liver extract.[1, 2, 3, 4, 5] However, this intravenous therapy is not in general use because of the side reactions noted in many cases.

The case of pernicious anemia reported in this paper is of interest because on the first admission the patient responded in a characteristic manner to the administration of liver extract intramuscularly and subsequently he had a relapse. On further treatment a progressive aplastic state continued despite the administration of oral liver, intramuscular extract, ventriculin and blood transfusions. Finally liver extract given intravenously resulted in a prompt and complete remission.

CASE REPORT

E. L. J., white farmer, aged 62, admitted to the hospital on November 19, 1934, complaining of weakness and generalized aching of three weeks' duration. Five years before his admission, while working for the State Highway Department he noted an increasing weakness which progressed finally to the point of difficulty in walking. There was no numbness or tingling. He was admitted to a Washington hospital where a diagnosis of pernicious anemia was made and he began taking liver by mouth. After a year's rest he was again employed and continued work for eight months. At the end of this period he reported that while cranking a car he felt something "give way inside of him," and that he had been unable to work since then. The patient's therapeutic regime was now changed to liver extract per os and later it was given intramuscularly. His treatment had been most irregular and he described periods of weakness coinciding with the times in which he had no therapy. Three years ago a lumbar puncture was done and he stated that he has been unable to walk since that procedure. Four blood transfusions had been administered during the past year. Three weeks before admission his local physician advised hospitalization because of weakness, palpitation of the heart and poor appetite.

The physical examination revealed an undernourished, elderly, pale man. The mucous membranes were pale and the sclera lemon tinged. The tongue was smooth and glistening. The heart, lungs and abdomen were normal. The blood pressure was 110 mm. of Hg systolic and 45 diastolic, pulse 112, and there was slight pitting edema of the shins. A bilateral hydrocele was present. The patellar reflexes were hyperactive, ankle clonus was present and there was a positive Babinski sign. The vibratory sense was absent below the knees. The patient could not walk.

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From the Department of Internal Medicine, University of Virginia Hospital.

Laboratory examinations showed the following: Hemoglobin 22 per cent (Dare), red blood cells 1,900,000, white blood cells 3,000, with band cells 4 per cent, segmented 51 per cent, small lymphocytes 43 per cent, large mononuclears 2 per cent. The platelet count was 137,000; the reticulocytes 1.5 per cent; color index .52; volume index .42; and the icterus index 15. The smear showed the red cells to have a marked anisocytosis with many microcytes, a few macrocytes, moderate poikilocytosis, and a moderate diffuse polychromatophilia was present. One normoblast was seen. No free hydrochloric acid was present in the stomach contents after the injection of histamine. The Wassermann and Kahn were negative.

From the history and findings a diagnosis of pernicious anemia was made and intramuscular liver therapy inaugurated. After one week of treatment the volume index changed to 1.2 and the color index to 1.2. The patient responded typically to this therapy as indicated in chart 1. Throughout his stay in the hospital he was

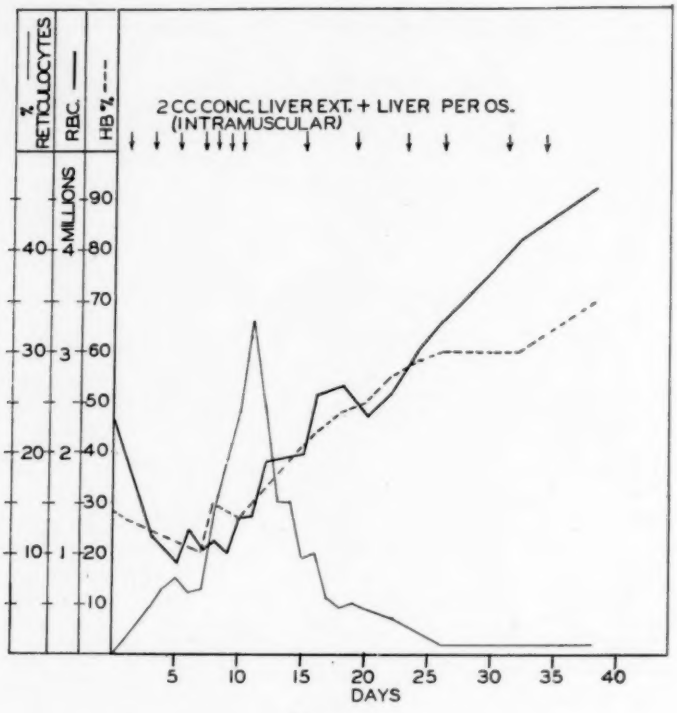

CHART 1.

given iron and ammonium citrate, 90 grs. daily. On discharge 41 days after admission he had improved in all respects, and he could move his legs without difficulty.

After leaving the hospital this patient took his liver extract intramuscularly (2 c.c.) once weekly for a while, then the interval between treatments became lengthened to every two weeks and finally once a month. He again became progressively weaker, with all of his old symptoms returning. On December 29, 1935, the patient was readmitted. In the period between the two admissions he had not been able to walk. The physical examination showed that the patient was again pale and thin. The blood pressure was 96 mm. of Hg systolic and 54 diastolic, and the knee jerks hyperactive, ankle clonus present with bilateral positive Babinski. On the whole he was in the same physical state as on the previous admission. Laboratory

examinations showed a hemoglobin of 35 per cent (Dare), red blood cells 1,740,000, white blood cells 2,800, and the differential essentially the same as on the last admission. The smear showed many macrocytes and a few poikilocytes. The color index was 1.3, volume index 1.4, reticulocytes 0.2 per cent, and the icterus index 10.5. A mild cystitis was also found to be present. A gastrointestinal roentgen-ray series was negative.

The patient was given 10 c.c. of concentrated intramuscular liver extract (Eli Lilly) followed by 2 c.c. of the same preparation every four days. In spite of this therapy there was very little reticulocyte response, the red count and hemoglobin decreased and the patient showed a progressive loss of strength and appetite. Parke Davis' intramuscular extract was then given and blood transfusions, liver by mouth and ventriculin were all tried with only temporary effect. Finally it was decided to give an intravenous preparation.* Twenty cubic centimeters were administered intravenously very slowly and this was followed by a chill and a temperature of 104° F. Following this the patient showed improvement in his condition, the reticulocytes rose and the blood picture in general showed evidence of the influence of the active principle in liver. On each subsequent injection of liver intravenously (five in all) the reactions became decreasingly severe with only slight flushing of the face and a little shortness of breath. Iron and ammonium citrate (90 grains daily) was given from the day of admission to the day of discharge. The essential data are given in chart 2. The patient was discharged 120 days after

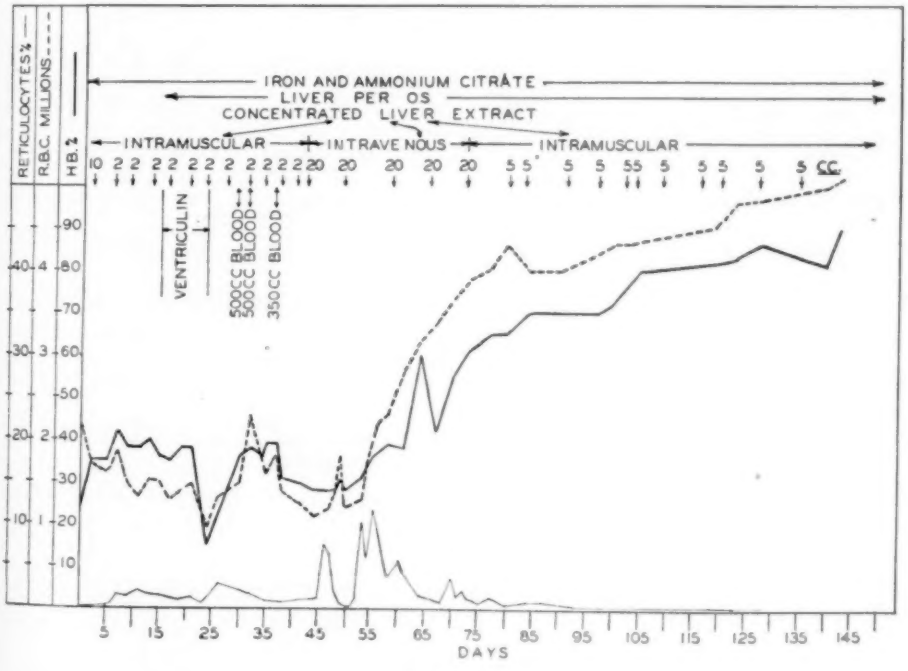

CHART 2.

admission in good general condition, with a normal blood count; but he was still unable to walk. He is being maintained at home in a good state of health with a normal blood picture by an intramuscular injection of 2 c.c. of liver extract once a week.

*An intravenous extract prepared by Parke Davis Co. was obtained through the courtesy of Dr. Raphael Isaacs, Ann Arbor, Mich.

Comment

In a review of the literature no mention was found of a similar case of pernicious anemia. Rhoads and Miller [6] cite two cases of sprue that failed to respond to intramuscular extract but recovered promptly when the extract was given intravenously. Castle et al.[7] also emphasize the importance of intensive parenteral therapy in this condition. One can only speculate with respect to the failure of this patient to respond to the usual therapeutic procedures used in treating pernicious anemia. The only evidence of infection was found in the bladder and it seems doubtful that this was sufficient to prevent an adequate response.

Minot [8] has called attention to the importance of adequate quantitative treatment in pernicious anemia, and it is possible that in this case the amount of liver used was not sufficient even when given intramuscularly. The only alternative explanation that can be offered is that the extract was not utilized which seems doubtful in view of the subsequent control by the intramuscular preparation. It is thought, however, that the case presents a method of dealing with an interesting therapeutic problem which might be useful in similar situations.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

FAMILIAL SHIFT TO THE LEFT OF THE LEUKOCYTES (PELGER'S NUCLEAR ANOMALY OF THE LEUKOCYTES), WITH REPORT OF A CASE *

By WILDER TILESTON, M.D., *New Haven, Connecticut*

IN 1928 Pelger [6] reported to the Dutch Pathological Society at Amsterdam two cases showing an anomaly of the leukocytes, hitherto undescribed in the literature. The neutrophiles, eosinophiles and basophiles all showed a large percentage with non-segmented nuclei, and the segmented forms were represented almost exclusively by those with only two nuclei. Furthermore, the nuclei differed from those met with in the ordinary shift to the left of infectious diseases, in that they had a remarkably regular shape with even contours. The protoplasm of the neutrophiles on the other hand showed fine even granulations, of the type seen in mature cells. His first case was a woman who suffered from cachexia of obscure origin, and died of a terminal pulmonary infection; there was no autopsy. His second patient was a man with splenomegaly; material obtained by puncture of the spleen was injected into a guinea-pig and caused tuberculosis in the animal. Pelger believed that the anomaly of the leukocytes was pathological, in some manner connected with tuberculosis, and of bad prognostic import.

Three years later Huët [4] discovered a similar hemogram in a niece of Pelger's first patient, and investigating other members of the family, found it in them also. He was therefore the first to recognize the familial character of the anomaly, and since it was present in healthy people, he declared it to be without pathological significance. Huët also reported two other families with this condition; there was no interrelationship between these families.

Other reports soon followed, so that up to the present time there have been recorded five such families in Holland, three in Germany, one each in Switzerland, Czechoslovakia, and the United States. It has been shown that the anomaly is inherited as a dominant Mendelian character, not sex-linked.

The following case, taken from the writer's private practice, seems worthy of record. It is the second to be reported in this country, and the first involving a person of English ancestry, Peterson's [7] publication having concerned a Chinese family.

CASE REPORT

The patient, a lawyer now 73 years of age, has been under the writer's care for the past 26 years. In January 1918 he had an attack of lobar pneumonia of moderate

* Presented at the Annual Meeting of the Association of American Physicians, May 5, 1937.

severity, with high fever and terminating by crisis; the leukocyte count was 16,600 with 82 per cent neutrophiles. In November 1918 he had influenza, with a temperature of 103 degrees and a leukocyte count of 3,500; no differential count was made. These facts are interesting as indicating a normal reaction to infection on the part of the bone marrow.

For the remainder of this long period he has had no serious illnesses, and is now in good health and active in the practice of his profession.

Five years ago he had an attack of syncope, the cause of which was undetermined, and a routine examination of the blood disclosed the fact that, although there were no signs of infection and the total leukocyte count was normal, more than half of the neutrophiles were non-segmented or staff forms, and that the nuclei of the remainder had, almost without exception, only two lobes. This curious condition has persisted ever since, with little change in the relative proportions (table 1). Most

TABLE I

Date	Red Cells Millions	Hgb. %	Leukocyte Count	Neutrophiles		Lymphocytes	Monocytes	Eosinophiles	Basophiles
				Staff Cells	Segmented Cells				
11–18–31	4.4	70	8,600	34	26	22	9	9	0
12–18–31	4.9	75	7,100	26	16	39	11	8	0
1– 6–32	—	—	—	34	24	17	15	10	0
3–15–32	—	75	6,200	46	16	30	5	3	0
6–13–32	—	75	6,000	43	19	29	4	5	0
12– 5–32	—	70	7,700	47	17	23	4	9	0
5–13–33	—	75	5,300	32	24	36	6	2	0
10–13–33	—	80	5,000	36	15	33	12	3	1
7–31–34	—	80	5,800	32	21	30	10	4	3
4–18–35	—	80	—	36	30	25	4	5	0
11–11–35	—	80	—	36	25	29	8.5	1.5	0
11–11–36	—	80	—	32	22	30	10	5	1
4–28–37	3.4	75	6,100	38	24	27	8	3	0
6– 2–37	4.7	88	7,800	43	21	27	5	3	1

of the smears have shown no nuclei with more than two lobes; rarely one with three lobes has been present (up to 1.5 per cent in the differential count), but never any with more than three lobes.

The appearance of the nuclei of the neutrophiles is unusual, the contours being smooth and regular, in contrast with the irregular shapes seen in the ordinary shift to the left, and in normal blood. A fair number of the non-segmented forms (up to 12 per cent of all neutrophiles) might be classified as "juvenile," by reason of their broad kidney-shaped nuclei; no myelocytes were encountered. The segmented cells have two oval or round nuclei, connected by a fine thread.

The protoplasm of the neutrophiles shows no abnormalities, toxic granulation and vacuolization being uniformly absent.

The eosinophiles are affected in a similar way, but to a less marked degree, a differential count of 100 eosinophiles showing 38 per cent non-segmented, 62 per cent two-lobed, none with more than two lobes. It should be noted that in normal blood segmentation of the eosinophiles is not carried out to the same extent as it is in the case of the neutrophiles, 76 per cent having two nuclei, and only 19 per cent more than two. However, staff cells normally make up only 3 per cent of the total, according to Zündel.[10]

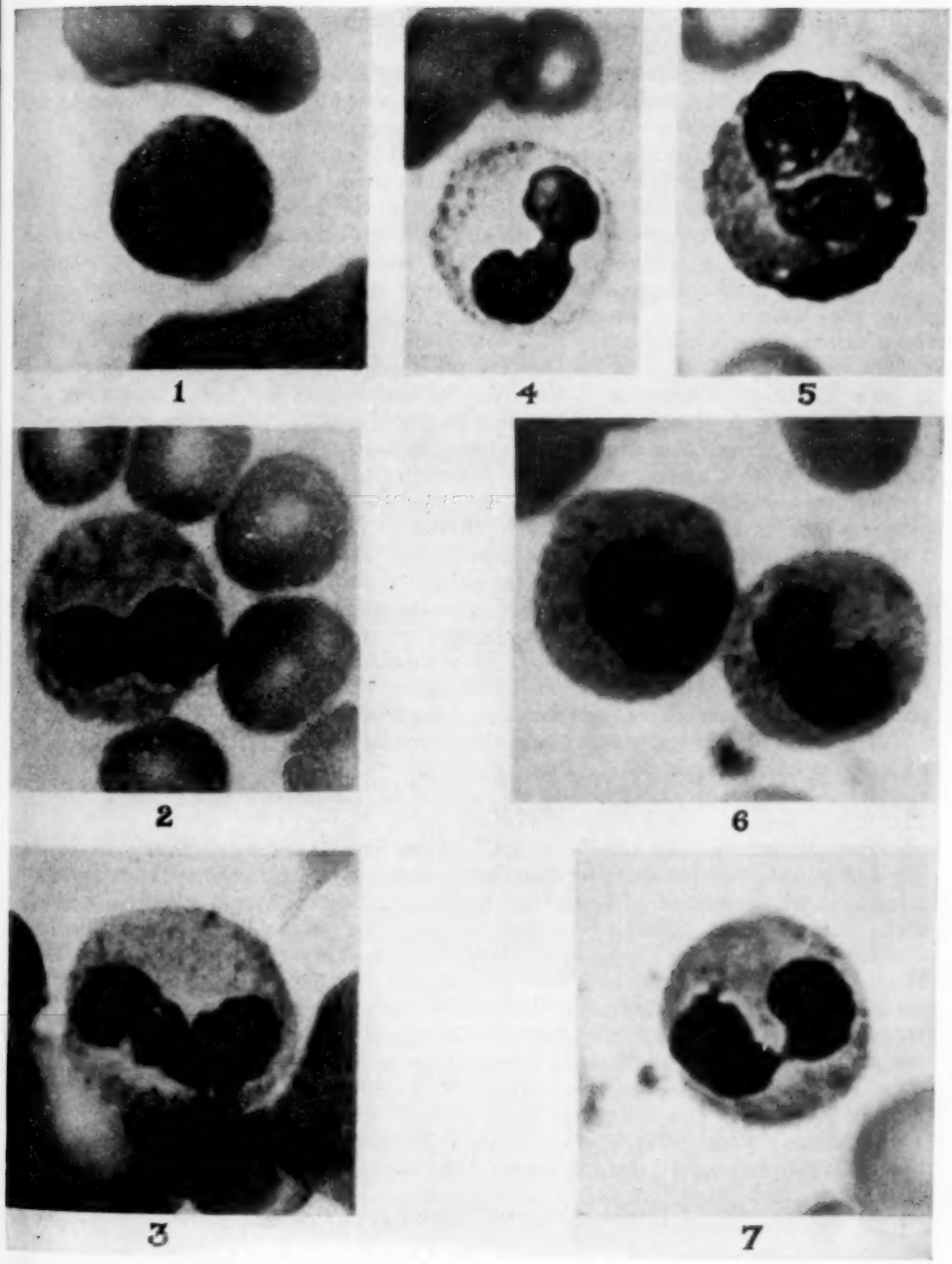

FIG. 1. Photomicrographs of polymorphonuclear leukocytes. No. 5 shows an eosinophile, others are neutrophiles. Leishman stain, magnification approximately 800.

It was difficult to determine whether the basophiles were involved or not, on account of the scarcity of these cells, and their frequent failure in normal blood to show clear-cut segmentation into several nuclei.

When treated with Goodpasture's stain, all of the neutrophiles showed abundant oxidase granules. In a supravital preparation examined by Dr. R. M. Thomas, all of the granulocytes showed motility, and no abnormal granulations were present.

An attempt to estimate the phagocytic activity of the leukocytes, made by Prof. George H. Smith, disclosed an interesting phenomenon, hitherto undescribed in this condition; on centrifugation of the oxalated blood, the leukocytes gathered together into a sticky mass, so cohesive that it was impossible to draw them up into a pipette, or smear them on a slide. No explanation of this curious behavior was forthcoming.

The differential count was normal, so far as lymphocytes, monocytes and basophiles were concerned. A tendency to eosinophilia (up to 10 per cent) was present, for which no cause was apparent; it is interesting to note that a grandnephew of the patient, otherwise healthy and not showing the anomaly, had 18 per cent eosinophiles. In some of the cases reported in the literature eosinophilia has been present but not often enough to suggest any connection with the anomaly.

The red count, hemoglobin, and total leukocyte count were within normal limits, apart from a trifling anemia, and the red cells showed no abnormalities. The platelet count was 240,000, the reticulocytes numbered 0.8 per cent. The coagulation time was 8 minutes, the bleeding time 1½ minutes. The patient's blood group is "A" (international nomenclature). The sedimentation rate was not determined.

Investigation of the relatives of the patient was disappointing. He has had no children, and both his brothers are dead. Examination of smears of all the children and grandchildren of these brothers, to the number of eight, and of two cousins, failed to reveal the anomaly in any of them. It is therefore impossible to state positively whether the condition in this person is familial or not, but since all of the cases reported in the literature have been familial, it may be assumed that it is.

The family history reveals a tendency to arterial disease. One brother died at 50 of a ruptured aneurysm of the iliac artery, the result of atheroma, the other died suddenly, of coronary occlusion, at the age of 57. The only sister was still-born. The father, however, lived to the age of 96.

Physical examination, April 22, 1937. Age 73 years. A tall thin man weighing 148 pounds. Color fair, pupils equal and react to light, arcus senilis present, sclerae faintly yellowish. Mouth and throat negative. Thyroid gland and lymph nodes not enlarged. Heart of normal size, action regular; there is a rather loud systolic murmur in the aortic area, transmitted towards the neck. Pulse rate 56, blood pressure 104 systolic and 58 diastolic; the peripheral arteries are moderately thickened. Abdomen natural, liver and spleen not enlarged. Knee jerks and plantar reflexes normal. On the skin of the neck and upper part of the chest anteriorly there are numerous rounded or flattened papules of a yellowish-white color; a biopsy was done, and a diagnosis of multiple benign cystic epithelioma was made. The urine is negative. Wassermann and Kahn tests of the blood negative. Blood group "A" (international nomenclature). The patient has shown a pronounced arcus senilis and a systolic murmur in the aortic area since the age of 47 years.

Discussion of the Literature

The blood picture as first discovered by Pelger has been verified by all subsequent observers. Unfortunately Pelger's description is not to be found in print, except as quoted by some of the Dutch writers, for the account of his original communication to the Dutch Pathological Society [6] merely alludes to a demonstration of two patients with a rare anomaly of the

leukocytes, without any description of the blood picture; the promised extensive article on the subject never appeared. Staff cells have been present in large numbers in all cases, and have almost invariably exceeded the segmented forms. Cells with more than two nuclei have been found rarely, or not at all. The shift to the left has gone as far as juvenile cells, but myelocytes very seldom have been noted, and then in small numbers (0.5 per cent, Schilling). The proportion of juvenile cells has varied widely, as might be expected on taking into account the element of subjectivity in the classification of this form of cell. Schilling, on examining smears from 11 cases, found the juveniles making up the majority of the non-segmented cells, but Undritz recorded only from 2 to 9 per cent.

All authors are agreed that the eosinophiles are involved in the shift, but as regards the basophiles opinions are divided. No extensive studies of the basophiles have been made.

Toxic granulation of the protoplasm of the neutrophiles has been absent, except in one of Zündel's cases.

The response to infection has been reported only in one instance; in one of Huët's cases during an acute unspecified infection the percentage of staff cells rose from 26 to 44 per cent.

No studies of the bone marrow have been made, nor have any autopsies been performed.

The sedimentation rate has been normal in all the cases in which it has been measured, in contrast to the increased rate met with in the infectious shift to the left.

Blood grouping seldom has been determined; Jordan's patient belonged to group "O," the writer's to group "A."

The familial character of the anomaly has been proved in all the cases reported up to the present time, with the exception of Pelger's second patient, and the case of Chevallier and Élÿ,[3] in both of which the relatives were not investigated. The trait has been found present in three generations by Huët, Jordans * and Peterson. It has been transmitted by both sexes, and males and females are affected in equal proportions (exactly 50 per cent of each). It is therefore not sex-linked. In no case have the offspring of unaffected members shown the anomaly. The proportion of the affected among the children of affected parents has varied from 50 to 100 per cent; Alieff and Reekers found 7 out of 14 affected, Huët 3 out of 6, Jordans 6 of 9 in the second generation, 3 of 6 in the third, Zündel 4 of 6, and 3 of 4 in the second and third generations respectively. The highest incidence was in the family of Undritz, in which all of 5 living members of the second generation were affected (two had died without investigation), and all of 3 siblings in the third generation. In no instance have both husband and wife been proved to be bearers of the trait.

* Jordans' family is identical with family "Q" of Burger; the family tree is completed in Burger's article.

It is thus apparent that the anomaly is a dominant Mendelian character, not sex-linked.

A large majority of the affected persons have been healthy, and there is no evidence that there is any unusual tendency to disease in these families. Many of them have had members who were tuberculous, but this may be accounted for by the ubiquity of this malady, and by the fact that the anomaly is more likely to be detected in the case of tuberculous patients in sanatoria, because of the periodical examinations of the blood which are made there. The Wassermann test has been negative in all of the cases in which it has been done. The association with hyperthyroidism in Peterson's family (5 cases) is unique in the literature.

The occurrence of this anomaly exclusively as an inherited trait indicates that the segmentation of the nuclei of the neutrophiles and eosinophiles is regulated by a constitutional factor. When this becomes modified by the process of mutation, the anomaly takes place, and is transmitted to the descendants as a dominant character.

Diagnosis. The diagnosis can be made from the stained smear by one who is familiar with the condition, on the following points: (1) The even contour and tendency to kidney shape with rounded ends on the part of the nuclei of the staff cells; (2) the failure to find neutrophiles with more than two nuclei; and (3) the absence of toxic granulation. In all of these respects the blood picture differs from the infectious shift to the left. In case of doubt the absence of signs of infection in the patient, and investigation of the relatives will clarify the situation. Failure to recognize the condition may lead to a serious mistake in prognosis.

The anomaly might be of medico-legal importance, as regards questions of identity and paternity.

Prognosis. From the evidence available, it appears that the health of persons with this anomaly is not adversely affected, and that their leukocytes are adequate so far as function is concerned.

Summary and Conclusions

1. A case of familial shift to the left of the leukocytes is reported, in which no other members of the family were found to be affected, probably on account of the lack of direct descendants.

2. The typical blood picture was present, viz., a high percentage of staff cells, mostly of crescentic or kidney shape; absence or extreme rarity of segmented forms with more than two nuclei; even contour of the nuclei, and absence of toxic granulation.

3. The literature is discussed.

The writer extends his thanks to Dr. R. M. Thomas and Prof. George H. Smith for assistance in the blood studies, and to Professor J. G. Dusser de Barenne for translating the Dutch articles.

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CASE REPORTS

TRANSVERSE MYELITIS FOLLOWING MUMPS*

By A. C. Fortney, M.D., *Fargo, North Dakota*

Although it is not unusual to find meningitis, encephalitis, neuritis, and delirium as complications of mumps, myelitis is most uncommon. Woltman and McKaig reported such a case in 1933, and at that time a very close search of the literature revealed only one other case, that of Warrington's reported in 1914. However, a third case was reported by Kuligowski in October 1933. I should like to add another to those reported.

Case Report

Mr. N. E., white male, aged 39, hardware dealer, first contracted mumps on December 26, 1935. Involvement first appeared in the right parotid, and four days later the left side became swollen. Mild bilateral orchitis developed, but rapidly subsided. His symptoms were mild. Delirium, headache, and neuritis did not appear. He did not feel sick enought to remain in bed longer than two days. On the evening of January 6, 1936, twelve days after the onset of the mumps he first noticed a little tingling in the soles of both feet. He had had no headache nor any pain in the neck or back. By the afternoon of January 8 his legs were so weak that he had to hang onto chairs or the wall to keep from falling down. By this time the tingling in the soles of the feet and legs had given away to a numb feeling. At this time, it had been 16 hours since he had urinated, and 24 hours since his bowels had moved. In spite of this he had neither the desire to urinate or defecate, nor did he experience any pain in the region of the bladder. Large doses of patent cathartics failed to move his bowels.

The next morning, January 9, his family physician was called who catheterized him, and obtained a large amount of urine which was not measured. A large soapy enema was given but had to be siphoned off as the patient was unable to expel it. His temperature was 100° F., pulse 84 and white blood cells 10,500. The patient was then moved to a hospital, where I saw him in consultation with Dr. O. S. Craise of Towner, North Dakota, on January 10. A spinal puncture on admission revealed clear fluid under normal pressure. Five cells were counted and there was a trace of globulin.

Past History. He had never had mumps until the present attack. He had had the other usual childhood diseases without any complications. He had had no serious illnesses, injuries, or operations.

Family History. Father died of arteriosclerosis. Mother living and well. Three brothers are living and well. No history of cancer, tuberculosis, diabetes, or insanity.

Physical Examination. The patient was a well developed and nourished white male of apparent age lying quietly in bed in no distress. The respirations are free and easy, cyanosis is absent and orientation is normal. The entire physical examination except as related to the nervous system is negative.

* Received for publication February 26, 1937.

From the Department of Internal Medicine, Hanna, Clay and Lancaster Clinic, Fargo, N. Dak.

Neurological Examination. The pupils are equal and regular and respond normally to light and accommodation. The fundi are normal. Extra ocular movements are normal. The patient has noticed no diplopia. The ears are normal, and hearing as tested with a watch is normal for both ears. There is no demonstrable weakness of the facial muscles. Sensation to pin prick, cotton, heat and cold over the face, neck, and scalp is intact. The tongue protrudes in a straight line and the gag reflex is present. There is no difficulty in swallowing water or solid foods. There is no weakness of the sternocleidomastoid muscles. There is slight rigidity of the muscles of the neck to anterior flexion. There is no swelling of the parotid glands.

Sensation, motor power, and reflexes are normal in the upper right extremity. There is a slight but definite weakness of the entire upper left extremity to all movements. The biceps and triceps reflexes are hyperactive. Sensation to pain, light, touch and temperature changes is slightly impaired in this member.

At the level of the third rib, diminution of sensation to pain, light touch and temperature begins to appear. From the level of the fifth rib and downward, these sensations are completely lost. The abdominal and cremasteric reflexes are absent. On auscultation of the abdomen, peristalsis is noted, and seems to be of normal intensity.

Both lower extremities are completely flaccid, and all superficial sensation is lost. Deep sensation is present. The patellar and ankle reflexes are weak. Patellar and ankle clonus is absent. There is bilateral positive Babinski and Oppenheim. On the right, position sense for the toes is normal, but erratic on the left. There is complete loss of bladder control. The rectal sphincter is toneless and the rectum remains widely opened after digital examination.

A spinal puncture was performed without anesthesia, the patient being aware only of a pressing feeling in the back. The fluid was clear and under 10 mm. of mercury pressure. On jugular compression the pressure promptly rose to 24 mm. and when released, promptly fell to its original level. Fifteen c.c. of the fluid were removed and the neck rigidity which was previously noted completely disappeared.

A diagnosis of transverse myelitis, probably due to the virus of epidemic parotitis, was made. It was felt that the outcome depended entirely upon the degree of permanent damage to the cord which only time would tell. It was further felt that cystitis and possibly pyelitis would result from the frequent catheterizations, and that this factor would be the most important in determining whether or not the patient would survive. Absolute bed rest, abstinence from any passive manipulations until improvement began, and splinting of flaccid extremities were ordered. Rigid attention to the care of the skin was emphasized. No medication was ordered except that necessary for intermittent alkalinization and acidification of the urine.

Progress. In the next few days the left arm became practically useless and flaccid. Following this there was very little change in the patient's condition up to the time he was discharged from the Hospital, on February 13, 1936. The only sign of return of function at that time was the ability to move the great toe on the right foot. The hospital regime was continued at home and gradual improvement began.

I next saw him on May 3, 1936. At the time he was in the best of spirits, and thoroughly convinced that he was going to get well. Power in the left upper extremity was now comparable to that of the right. He was able to come to a sitting position in bed without any assistance. The abdominal reflexes and cremasteric reflexes were sluggish. A rounded, rather tense, painful mass appeared above the symphysis to a point half way to the umbilicus. This was a distended bladder. The patient was able to move in any direction in bed without aid. However, on determining the strength passively in his legs it was still found to be much diminished; in the left more so than in the right. Astereognosis and adiadokokinesis were absent. Position sense of the toes was normal. Sensation to pin pricks, cotton, and tem-

perature changes was practically normal over the entire body. A specimen of urine was bloody. Patient was having a definite overflow type of urination, and was still being catheterized daily. It was evident that a severe cystitis was present. The temperature showed daily fluctuations, going as high as 100.5° F.

The remainder of the physical examination was normal. At that time it was evident that the patient was making very satisfactory progress in every way except in regard to the urinary tract infection. The risk of a general infection was still a definite one. In July 1936, he returned to the Hospital and a cystotomy with supra pubic drainage was done. Since then his urinary infection has cleared up considerably and now he has complete control of the bladder and bowels. He is able to walk around with practically no difficulty. The patient may be classified as a completely recovered case.

Summary

A case of myelitis following mumps is presented. The rarity of the entity is made note of, there being only three other cases reported in the available literature. This case corresponds very closely as to time of onset, symptoms and clinical findings to those reported by Woltman, Warrington and Kuligowski except for the absence of back pains.

The prognosis in this type of complications must be guarded. In the four cases reported, one died on the ninth day of illness; one showed no improvement 19 months after onset; one was completely well at the end of eight weeks, and the case reported here showed complete recovery at the end of seven months. Only conservative treatment was instituted. However, the use of convalescent serum intra-spinally and intra-venously and the employment of frequent spinal puncture might well be given a trial in such instances of spinal cord involvement following mumps.

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INTERNAL HYDROCEPHALUS FOLLOWING REPEATED INTRAVENTRICULAR HEMORRHAGES*

By Francis J. Scully, M.D., F.A.C.P., *Hot Springs, Arkansas*

Spontaneous intraventricular hemorrhage is quite rare and when it occurs is usually promptly fatal. A recurrence of such a hemorrhage is therefore quite unusual. The following case is especially interesting because of the development of an extensive internal hydrocephalus following repeated intraventricular hemorrhages.

Case Report

Mrs. J. S., aged 60, was seen in consultation with Dr. H. A. Ross of Arkadelphia on November 1, on account of a persistent headache and dizziness. On October 16

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the patient had suddenly dropped over unconscious while sewing. She had previously felt well, and that morning had eaten breakfast as usual. She remained comatose for about 15 minutes. Following this attack she had developed headache, which gradually became more severe and had continued since. She required morphine, bromides, and amytal to keep her comfortable. The headache was persistent and extended down into the back of the neck. For three days there was rather marked vomiting and the vision became blurred. These symptoms had shown improvement until on October 31, when she had two mild convulsive attacks with some movement of the right arm over the chest. At the onset of the illness the blood pressure was 180 mm. of Hg systolic.

The patient had had influenza five years before. A panhysterectomy had been performed 20 years before on account of a tumor of the uterus, which was thought to be cancerous. She had borne six children, five of whom are living.

Examination showed the patient to be rather pale and in a semi-stupor. The heart and lungs were normal. Blood pressure 160 systolic and 80 diastolic, pulse 60, temperature 98.4° F. The peripheral vessels showed a moderate sclerosis. The pupils were small and equal, and reacted only slightly to direct light, due to opiates. Ophthalmoscopic examination showed a choking of both discs. The tongue was extruded in the midline. The deep reflexes were active and there was no paralysis or sensory changes in the extremities.

Laboratory tests showed hemoglobin 60 per cent, red blood cells 3,280,000, and white blood cells 10,100. The Wassermann test was negative on both the blood and the spinal fluid. The spinal puncture yielded fluid under increased pressure, showing a heavy trace of globulin and many red blood cells. The fluid was of a golden yellow color, but did not clot on standing.

From these findings it was thought the patient had a brain tumor in which a hemorrhage had occurred, and that the convulsive attacks had appeared during the period of active bleeding. Since there were no localizing symptoms, and since there had been a period of recovery after the first hemorrhage, it was thought best to keep her quiet in bed and to use sufficient sedatives to control the discomfort, in the hope that the bleeding would subside and that immediate surgical intervention would not be required.

During the month of November the patient improved. There were several mild attacks but no stupor following them. There was improvement in the vision and when seen by Dr. O. H. King, on November 20, the eye grounds were normal.

On December 2 the patient had a severe convulsive attack, with gradually increasing stupor, which continued until she died.

Autopsy: The brain was removed and examined by Dr. D. C. Lee, who reported that on section the brain showed a marked internal hydrocephalus. The lateral ventricles were markedly dilated and the septum between them was obliterated. The third and fourth ventricles were also dilated. All the ventricles were filled with clotted blood. There was some blood extending out from the fourth ventricle on the base of the cerebellum. The corpus callosum was very much thinned and the dilated ventricles measured 10 by 5 cm. at the base of the anterior horn. In the anterior horn of the right lateral ventricle there was a spongy mass about 4 cm. long and 2 cm. wide. It was attached loosely to the inner and lower wall of the ventricle at the anterior portion of the choroid plexus. No tumor mass could be found. On microscopic examination the mass proved to be an organized blood clot, with a number of dilated vessels of the choroid plexus included.

Discussion

From the pathological findings it was evident that this patient had had repeated hemorrhages from the anterior portion of the choroid plexus in the right

lateral ventricle and that the bleeding had been sufficient each time to fill the ventricles with blood causing an internal hydrocephalus. The blood pressure was above normal which made the hemorrhage more likely to occur. The convulsive attacks occurred with each repeated hemorrhage. When the spinal puncture was made in November the golden yellow color was due to the previous hemorrhage, and the red cells found were probably due to the hemorrhage that had occurred the day before. With each hemorrhage there would be sufficient pressure on the brain to produce the convulsion, and to cause the interference with vision which was noted. With the absorption of the blood these symptoms would subside. The organized clot of blood was a further indication of the repeated hemorrhage and of the attempt of the body to control the bleeding. The last hemorrhage was so marked that the vital centers of the brain were too depressed for the individual to survive.

Intraventricular hemorrhage is not uncommon in severe traumatic injuries to the head and brain. In newborn infants it also occurs more often than is generally suspected. Hemsath [1] reports its occurrence in 4.8 per cent of a series of 414 autopsies of still born and newborn infants. Occasionally in massive cerebral hemorrhages the bleeding will extend from the internal capsule into the ventricle.

Spontaneous intraventricular hemorrhage having its origin in the ventricle is quite rare. Copeland [2] reports one case in a man, aged 51, with arteriosclerosis and hypertension. The hemorrhage had its origin in the walls of the aqueduct. Sands and Lederer [3] reported three cases, two with arteriosclerosis, and one with intracranial aneurysm. They state that the diagnosis of intraventricular hemorrhage is very difficult even under the most ideal conditions. A good review of the symptoms in these cases is given in their article.

Apparently intraventricular tumors do not give rise to hemorrhage as often as one would suppose. Dandy,[4] in 1933, reported 13 cases of benign tumors in the ventricle, and reviewed 25 additional cases from the literature. In one of his cases a venous aneurysm in the wall of the ventricle was removed after a second hemorrhage had occurred in the right ventricle. Eight additional cases were reported in 1934 by Fincher,[5] but none of them were accompanied by hemorrhage.

In the case reported above it was not possible to determine whether there was an aneurysm of the vessels of the choroid plexus at the point where the hemorrhage occurred. On microscopic section it was noted that the vessels were very thin and dilated where they were a part of the organized clot of blood. It is possible that these thin vessels had ruptured with some sudden increase of the blood pressure, which was already high, and that the clot which formed was not sufficient to prevent subsequent bleeding.

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EDITORIAL

CERTAIN TOXIC EFFECTS OF SULFANILAMIDE

Many men in the past months have likened in their minds the present era in the treatment of infections to that period of excitement which immediately followed the first clinical use of Ehrlich's "606." Indeed many have felt that in the new drug, sulfanilamide, the medical profession had obtained a therapeutic agent of greater importance to humanity than even salvarsan itself.

So chastened are many medical men as a result of repeated chemotherapeutic disappointments that the earlier announcements of the striking influence of this drug on certain coccal infections were met with a certain degree of cynicism. A larger number, however, not only readily accepted the value of the drug in streptococcal infections but, forgetful of the bitter lessons of cinchophen, amidopyrine, and dinitrophenol, promptly hastened to try the drug in every conceivable condition without heed of possible danger. The therapeutic reports already at hand must convince the most skeptical of the undoubted value of this potent new remedy. It is almost breath-taking to read of the results obtained in such highly fatal conditions as streptococcus meningitis, streptococcus septicemia, puerperal fever and in meningococcus meningitis. On the other hand there is no doubt that the drug exhibits toxic effects and that in some cases these may be of a serious nature. There is a wealth of recent reports on these toxic manifestations. It is important, therefore, for every man in the practice of medicine to be able to weigh carefully the relative advantages and disadvantages of the employment of this drug.

Whatever is written concerning the subject of sulfanilamide today may well be out-dated or contradicted by the contents of next month's medical journals, but at the moment it would seem that while there is a highly varied set of toxic manifestations which may follow the use of this chemo-therapeutic agent, yet on the whole we have reason to think that for the most part they are minor in nature and that even those of a more threatening type can apparently be successfully combated. It must be borne in mind, however, that for the most part reports have dealt with the immediately acute effects of the drug resulting from short courses of its administration. Whether, later, more serious injuries may be reported as a result of its prolonged use, or whether delayed reactions may become manifest at a later period in those who have apparently utilized it without harm, remains to be seen.

A great deal of interest is attached to those toxic effects involving the skin. Not far from one in twenty of the patients receiving this drug develop a rash. The most usual form of eruption resembles measles rather closely; there may be mild constitutional symptoms, fever and malaise,

accompanying its appearance. The rash is most apt to occur after the drug has been taken for five days or more. It disappears fairly promptly upon discontinuance of the sulfanilamide but may recur if more of the drug is taken. Recently an interesting observation has been made by several authors [1, 2, 3] that a more violent form of eruption may occur in those who have been taking this drug, over such areas of the body as are exposed to sunlight. In certain of these cases there has been a marked swelling of the affected part, edema and infiltration of the skin, and large coalescent macules and papules of a pink to dusky red color. The skin condition may progress to a marked vesiculation. In convalescence it is followed by desquamation. With the onset of this severe eruption, there may be quite marked nausea, chills and fever. The nature of the photosensitivity in these cases has not been further investigated.

Cyanosis is very common in those taking the drug and its intensity is often quite alarming. There is still a great deal of confusion as to the nature of this abnormal coloration. Some have attributed it to the presence of methemoglobin; others to sulphemoglobin, but equally careful observers have been unable to find evidence of either of these forms of hemoglobin and they are inclined to believe that in certain instances, at least, there is a new abnormal compound formed in the blood which gives it its cyanotic color. The cyanosis is not accompanied by any evidence of distress on the patient's part and when because of the seriousness of the infection, the drug has been continued regardless of the patient's color no apparently harmful consequences have followed.

It has been discovered [4] that slight degrees of acidosis, as determined by a lowering of the CO_2 combining power of the blood, are present in a considerable proportion of patients taking sulfanilamide. Since in a few cases the degree of acidosis has been quite severe, it has been recommended that 10 grains of sodium bicarbonate be given with each dose of sulfanilamide.

Among the most striking and serious of the toxic effects which have been so far observed are those involving disturbance of the normal blood picture. Slight grades of anemia have been frequently noted, apparently as a consequence of full doses of the drug. Quite different, however, are the cases of acute hemolytic anemia [5, 6] which may come on very suddenly in patients taking routine dosages of this new remedy. Pallor, profound weakness, and

[1] MENVILLE, J. G., and ARCHINARD, J. J.: Skin eruptions in patients receiving sulfanilamide, Jr. Am. Med. Assoc., 1937, cix, 1008.

[2] GOODMAN, M. H., and LEVY, C. S.: Eruption during administration of sulfanilamide, Jr. Am. Med. Assoc., 1937, cix, 1009.

[3] FRANK, L. J.: Dermatitis from sulfanilamide, Jr. Am. Med. Assoc., 1937, cix, 1011.

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[5] HARVEY, A. M., and JANEWAY, C. A.: Development of acute hemolytic anemia during administration of sulfanilamide, Jr. Am. Med. Assoc., 1937, cix, 12.

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jaundice accompany the rapid fall in the red count. If the process is severe, the blood serum may be port wine color from the liberated hemoglobin and the urine a dark brown from hemoglobinuria. In a case recently seen the red count fell from 4.5 million to 700,000 in less than two days. Fortunately, cessation of the drug is apparently followed at once by cessation of the hemolytic process. Transfusions are very helpful in tiding the patient over the acute phase of the process. Cases observed so far have all recovered.

There has been a great deal of fear from the start that the drug might cause granulocytopenia. There have been a few undoubted cases and in one at least of these death was attributed to this complication of treatment. However, in most of the relatively few cases so far reported recovery has been prompt upon removal of the drug.

Patients taking the drug very usually notice some slight general symptoms of the nature of dizziness, slight headache and ringing in the ears. These may safely be ignored. More serious neurological effects such as have been described in experimental animals have not appeared in man. An exception to this rule is the case of a patient recently reported [7] who developed a toxic optic neuritis with severe temporary loss of vision. Fortunately, the recovery of this patient is apparently going to be complete.

It is well, of course, for the physician who contemplates using this drug to be aware of the nature of the toxic effects which may be produced. In certain instances these effects seem to be dependent to some extent upon the size of the dosage and the length of time it had been employed. There is some evidence that this is particularly true of the skin eruptions. On the other hand, the acute hemolytic anemia and the granulocytopenia appear to be due to idiosyncrasy. They may appear on normal dosage within the first few days after the drug has been started. It is not likely then that the occurrence of a certain percentage of these cases can be avoided.

It is believed that the use of sulfates, such as magnesium sulfate and ferrous sulfate simultaneously taken with sulfanilamide, predisposes to the formation of sulphemoglobin and perhaps to other complications. It has been suggested that paraldehyd diminishes the efficacy of the drug. A safe rule would be to avoid concurrent therapy with other medicinal preparations if this is feasible. The physician should recall too that sulfanilamide is excreted almost entirely through the kidney. When the renal apparatus is normal excretion of the drug is fairly rapid, and it is this rapid excretion, no doubt, which tends to cut short the toxic manifestations as soon as the intake of the drug is discontinued. On this account, however, the giving of the drug to a patient with chronic or acute nephritis carries with it a hazard that if toxic effects occur, they will perhaps be more prolonged and more serious than in the patient with normal excretory powers. It is certainly the part of caution also, that during the course of administration of

[7] Bucy, P. C.: Toxic optic neuritis resulting from sulfanilamide, Jr. Am. Med. Assoc. 1937, cix, 1007.

the drug, the patient should be kept at rest and under daily observation. It would be a wise rule also to warn all patients not to expose themselves to strong direct sunlight.

As in the case of all new remedies the physician is called upon to balance carefully in his mind the importance of the advantage to be gained by the use of the drug against the possible disadvantages of its as yet only partially known toxic effects. The conservative physician will not use this powerful remedy unless he is faced with a disease of dangerous character not equally amenable to other forms of treatment.

M. C. P.

REVIEWS

To Drink or Not to Drink. By CHARLES H. DURFEE. Longmans, Green and Co., New York. 1937. Price, $1.00.

This interesting and lucid book on the problem drinker deals with but one aspect of the chronic alcoholic problem. The author does not undertake to discuss those diverse pathological mental problems associated with or proximal to chronic alcoholism.

The book consists of 11 chapters, the last being an epilogue on the archaic attitude of the general public towards alcoholism. The popular attitude towards the chronic alcoholic has been to condemn and to make a moral issue. This popular conception, with its indignant attitude and vindictive outlook, stands in paradoxical relationship to the opinions of poets and philosophers who have sung of the joys of drinking down through the ages. These two paradoxical attitudes are broadly but forms of individual rationalization and probably bear a relation to the popular concepts respecting individual responsibilities involving choice of behavior. The author implies, however, that this popular concept must be replaced with a more scientific one of natural phenomena being an endless chain of cause and effect.

It is not possible to understand the nature and causes of wickedness, of the bad and the sordid, or the mean and the vile, or the abandonment of all those things by which men ordinarily live, if the approach is in the direction of intolerance and condemnation for alcoholism. The problem drinker cannot be understood, satisfactorily treated, or his condition ameliorated or prevented through an emotional outlook that is influenced by a spirit of vindictiveness or maudlin sympathy. With the above premise in mind the theme of this volume is perhaps expressed in the author's own words, thus, "Modern therapy of alcoholism takes its stand on practical grounds. Its effort to change conduct, unlike the miracle methods of old, are based on the hypothesis, confirmed by both research and common sense, that the behavior of an individual is the interaction of himself and his circumstances. If we recognize alcoholism as a symptom of some difficulty of the whole man and deal with it realistically we rob it of its terrors and offer freedom and happiness to countless harassed problem drinkers."

The volume is vouched for in a signed foreword by Dr. Arthur Ruggles, Superintendent of Butler Hospital, Providence, Rhode Island, who comments that the methods of approach to the problem drinker as outlined by the author are superior in many respects to those previously prevailing.

The author expresses the hope that the book may be of value to the family physician, the clergyman, the welfare worker and the public administrator, and all who come in contact with the drink problem. It is obvious that many family physicians are consulted from time to time concerning the best methods of approaching the problem drinker who is detrimental to himself and those nearest and dearest to him. In the use of this little book serious consideration might be given to the possibility of its being placed on the family physician's reading list for prescription to the problem drinker and those who come in contact with him, since the book affords many passages to stimulate reflection for the problem drinker to better know himself.

In analyzing the theme of this publication one somehow automatically turns to the writings of that great humanitarian, Charles Dickens, who said, "Who turns his back upon the fallen and disfigured of his kind, abandons them as vile, and does not trace and track with pitying eyes the unfenced precipice by which they fell from good, does wrong to Heaven and man, to time and to eternity."

W. L. T.

The Diagnosis and Treatment of Diseases of the Stomach and Intestines. By WILLIAM FITCH CHENEY, B.L., M.D. 378 pages; 15.5 × 24 cm. Oxford University Press, New York. 1936. Price, $5.50.

This volume is one of the Oxford series of "Monographs on Diagnosis and Treatment." The author has attempted to present the subject of the diseases and disturbances of the gastrointestinal tract in sufficient detail for practical use and still to avoid lengthy theoretical discussion. Certain subjects of interest to the specialist are necessarily omitted. The treatise is based on the author's own experience and contains very few references to the literature but the occasional authority to whom attention is called shows clearly that the volume is up to date. Moreover, the discussions of gastroscopy and gastrophotography give the same impression.

The book is divided into two parts, one devoted to "Diseases of the Stomach," and the other to "Diseases of the Intestines." Both parts are developed according to the same plan so that the second half of the volume, with certain exceptions, is a counterpart of the first. Throughout the volume the discussions are clear and concise. Case reports are presented briefly and so effectively that they may be said to illustrate the text.

Although the volume contains all the essential data necessary in the modern study and treatment of gastrointestinal disease it nevertheless is not a satisfactory reference book for the specialist. It probably was not meant to be. Furthermore, although it avoids controversy the writer's conviction that gastroptosis is associated many times with disturbances of digestion and that correcting the former removes the latter may be responsible for a good deal of debate.

By succinctly presenting the diseases under discussion and bringing them up to date with regard to diagnosis and treatment and by stressing the care that must be taken in localizing a pathologic change in the proper organ the writer has given us a splendid part of an excellent system of books.

S. M.

Treatment in Psychiatry. By OSKAR DIETHELM, M.D. 476 pages; 16 × 24 cm. Macmillan Company, New York, N. Y. 1936. Price, $4.00.

There are so remarkably few volumes devoted to the treatment of the mental disorders that such a one is very welcome. It is carefully and thoughtfully written. It is fundamentally sound.

It begins with a study of personality, followed by general principles of treatment, then proceeds to an exposition of suggestive and hypnotic procedures, psychoanalytic procedure, and the special psychotherapeutic variations of Adler, Jung, Trigant-Burrow, Rank and Stekel, Du Bois, and Kronfeld, as well as the indirect methods represented by association experiments and Rorschach's Tests.

Dr. Diethelm then presents his own general views (and those of Dr. Adolph Meyer's followers) in a chapter called Distributive Analysis and Synthesis.

The rest of the book consists of detailed examination of what he feels to be the primary considerations to be dealt with in each type of disorder. He tells how he handles these problems as they arise and illustrates with pertinent and well chosen case history briefs.

The whole presentation seems to us distinctly on the dogmatic side. In a work of this kind this is not a bad fault since it is designed to be used by physicians in general, who may not be too familiar with the diversity of views held by professional psychiatrists, but who are looking for concrete treatment programs to follow.

We feel it does not adequately stress the enormous therapeutic value of the simple rapport or physician-patient fellow-feeling relationship which leads to many recoveries regardless of any technics. It lays much too much stress on the use

of drugs, particularly sedatives. Here they would seem to hold a prominent if not preëminent place in every treatment program. They do have their usefulness—in selected cases—but we would have preferred to see the author sound a note of caution in their use.

We have always been curious as to the reasons why hypnosis receives as much attention as it always seems to, in view of the fact it is now so little used.

This book will naturally be of much more use to the psychiatrist than to physicians outside this especial field, but is probably the best treatment text in English which has so far appeared.

H. M. M.

Clinical Allergy. By LOUIS TUFT, M.D. 711 pages; 24 × 15½ cm. W. B. Saunders Co., Philadelphia and London. 1937. Price, $8.00.

This book is an eminently satisfactory manual of practical allergy. It should be useful to the general practitioner and student and, in addition, should prove of value as a manual of practical procedures for allergists and for technicians connected with allergy clinics.

Dr. Tuft, while giving the background of the subject and presenting the important points of its development together with the various views held, on different phases of the subject, is sufficiently dogmatic to make the text workable as a practical guide.

The arrangement of the book is quite satisfactory. He first considers the general principles involved, explaining the mechanism of anaphylaxis and allergy and giving the general principles of diagnostic and therapeutic methods. He next considers allergic conditions from an etiological standpoint. Under this section he discusses serum, drug, food, pollen, bacterial and physical allergy. The third section considers allergy from the standpoint of its clinical manifestations, taking up asthma, allergic rhinitis, gastrointestinal allergy and migraine.

His fourth section, which is called Allergic Dermatoses and Allergy in Relation to the Specialties should be most valuable to men in other fields, especially those interested in nose and throat diseases.

Not the least important portion of the book is the appendix. Here, Dr. Tutt covers the laboratory methods in anaphylaxis and in allergy, describing under the latter the passive transfer method of Prausnitz-Kustner, the preparation of liquid and dry allergenic extracts and the preparation of pollens for microscopic examination. He also gives practical, detailed directions for asthma and hay-fever patients. A very valuable feature is the list of the possible allergens in household materials and in foods, together with a list of allergens and their sources. There are allergic diets and recipes which should be most helpful and his bibliography should prove very valuable to anyone interested in the subject.

The book contains a moderate sized but valuable group of pictures. The author has avoided the inclusion of useless photographs which so frequently appear in texts of this sort.

A novel and valuable feature is the use of case vignettes to demonstrate and clarify clinical points under discussion.

The excellent section on pollen allergy leans heavily upon the work of Thommens (Coca, Walzer and Thommens: "Asthma and Hay-Fever in Theory and Practice") and the chapter on pollens written by O. C. Durham for Feinberg's "Allergy in General Practice."

In the opinion of this reviewer, Dr. Tuft's book is the most practical one so far written on the subject of allergy and should be of the greatest possible value to anyone interested in this field.

H. M. B.

Syphilis Sive Morbus Humanus. By CHARLES S. BUTLER. 137 pages; 23½ × 15 cm. The Science Press Printing Company, Lancaster, Pa. 1936. Price, $3.00.

This small volume has been written by the author as a summary of the evidence indicating, first, that syphilis was present in Europe long before Columbus and hence did not arise in America, and, second, that syphilis and yaws are different manifestations of the same disease. The results of prolonged historical research are evident on every page and the reader will be delighted by many picturesque quotations. The author's interest in his subject overflows into many allied fields so that topics such as the history of slavery are dealt with under sub-headings; and these diversions are almost always very interesting. Altogether the non-specialized reader will find enjoyment and profit in the reading of this little book and will acquire a broader view of the nature of the chief venereal infection.

M. C. P.

COLLEGE NEWS NOTES

Gifts to the College

Grateful acknowledgment is made of the receipt of the following donations to the College Library of publications by members:

Books

Dr. Charles Solomon (Associate), Brooklyn, N. Y.—"Formulary of the Jewish Hospital of Brooklyn"

Dr. August A. Werner (Fellow), St. Louis, Mo.—"Endocrinology: Clinical Application and Treatment"

Reprints

Dr. Nathan Blumberg (Fellow), Philadelphia, Pa.—one reprint, "Bronchiectasis—with Description of the Peri Nasal Method of Introduction of Iodized Oil for Diagnosis and Treatment"

Dr. Milton A. Bridges (Fellow), New York, N. Y.—ten reprints, "The Physician and Modern Dietetics"; "Modern Dietetics and the Practitioner"; "The Modern Approach to Diet Therapy"; "The Primary Contracted Kidney"; "Diet Prescription for the Tuberculous"; "A Simple Method of Apothecary-Metric Transcription"; "Fads and Fallacies Regarding Food and Diet"; "Chronic Mucous Colitis"; "The Relationship of Precordial Stress, Blood Uric Acid, and Salicylate Therapy"; "The Present Status of Nutrition in Relation to Disease"

Rear Admiral Charles S. Butler (MC) U. S. N. (Fellow), Washington, D. C.—four reprints, "Syphilis Sive Morbus Humanus"; "Who Gave the World Syphilis? And How!"; "The Importance of the Chancre in the History of Medicine"; "A Glance at Results of the 'Last Thirty Centuries' of Venereal-Disease Prevention"

Dr. Anthony C. Cipollaro (Associate), New York, N. Y.—two reprints, "Drug Eruptions"; "Electrosurgery in Dermatology"

Dr. Harold G. Trimble (Fellow), Oakland, Calif.—two reprints, "What Is a Preventorium Child?"; "Pneumoperitoneum in Treatment of Pulmonary Tuberculosis"

Dr. Willard R. Wirth (Associate), New Orleans, La.—one reprint, "Heart Disease and Pregnancy"

New Life Member—Dr. Charles W. Waddell (Fellow), Fairmont, W. Va., by subscription became a Life Member of the American College of Physicians on September 7, 1937.

Dr. Louis H. Fligman (Fellow and Governor for Montana for the College), of Helena, Mont., has been re-appointed a member of the Montana State Board of Health by the Governor of Montana. Dr. Fligman has served on the Board since 1919, and acted as President four different times.

Under the presidency of Rear Admiral P. S. Rossiter (Fellow), Surgeon General of the U. S. Navy, the Association of Military Surgeons of the United States held its Annual Convention in Los Angeles, October 14 to 16.

Dr. Julius H. Hess (Fellow), Dr. Robert A. Black (Fellow), both of Chicago, and Dr. Gerald M. Cline (Fellow), Bloomington, Ill., have been named by the Governor of Illinois as members of a newly created Advisory Board of the Division for Handicapped Children, Illinois State Department of Public Welfare.

Dr. Arthur C. Christie (Fellow), Washington, D. C., was installed as President of the Fifth International Congress of Radiology at Chicago during September.

Dr. Charles A. Waters (Fellow), Baltimore, was Chairman of one of the sessions on roentgen diagnosis; Dr. Albert Soiland (Fellow), Los Angeles, and Dr. Arthur U. Desjardins (Fellow), Rochester, Minn., were Chairmen of sessions on radiotherapy; Dr. George E. Pfahler (Fellow), Philadelphia, gave the Caldwell Lecture of the American Roentgen Ray Society on "Treatment of Carcinoma of the Breast." Dr. Pfahler also was an honorary vice president of the Congress. Dr. Benjamin H. Orndoff (Fellow), of Chicago, was general secretary.

Dr. William C. Menninger (Fellow), Topeka, Kan., delivered the Rogers Memorial Lecture on "Psychological Factors in Medical and Surgical Conditions" before the 96th annual meeting of the State Medical Society of Wisconsin, held in Milwaukee, September 15 to 17.

Dr. Logan Clendening (Fellow), Kansas City, Mo., was the banquet speaker at the above meeting, his subject being "The Great Centers of Medical Thought in the Past."

Dr. Louis Hamman (Fellow), Baltimore, was one of the speakers in a symposium on non-tuberculous lung conditions at the annual meeting of the Southern Tuberculosis Conference and the Southern Sanatorium Association at Richmond, September 29 to October 1.

Dr. Edward J. Murray (Fellow), Lexington, Ky., was President of the Conference.

Dr. Francis E. Harrington (Fellow), Health Commissioner of Minneapolis, was recently appointed a member of the Hennepin County Sanatorium Commission, to succeed Dr. S. Marx White (Fellow).

Dr. Samuel A. Levine (Fellow), Boston, and Dr. Cyrus C. Sturgis (Fellow), Ann Arbor, Mich., will be guest speakers on the program of the fall clinical congress of the Oklahoma City Clinical Society, November 1 to 4.

Dr. Edward L. Bortz (Fellow), Philadelphia, is Chairman of the Commission on Pneumonia Control of the Medical Society of the State of Pennsylvania.

Dr. Edward W. Bixby (Fellow), Wilkes-Barre; Dr. Clifford C. Hartman (Fellow) and Dr. George J. Kastlin (Fellow), Pittsburgh; Dr. Leon H. Collins, Jr. (Associate), Dr. T. Grier Miller (Fellow), Dr. Henry K. Mohler (Fellow), Philadelphia, are members of the Commission. County medical societies were asked to create pneumonia control committees to be represented at a meeting of the Commission in Philadelphia during early October, when a campaign for the fall and winter was planned. Points in the program will be to develop laboratories throughout the State for diagnostic typing and to have the State, in cases properly certified, furnish pneumonia serum to those unable to pay for it.

The advisory board of the Pennsylvania State Health Department, at a meeting in July, adopted a regulation making pneumonia a reportable disease.

Dr. C. Walter Clarke (Fellow), New York City, after completing his work with the New York City Department of Health, in the organization of its bureau of social hygiene, has returned to active duty with the American Social Hygiene Association as its Executive Director.

Dr. LeRoy H. Sloan (Fellow), Chicago, has been appointed full Professor of Medicine in the University of Illinois College of Medicine.

Dr. Cyrus C. Sturgis (Fellow), Professor and Head of the Department of Internal Medicine at the University of Michigan Medical School, has been appointed by the Dean to establish a clinic, and to supervise its operation, newly established at the University Hospital, Ann Arbor, through the Rackham Fund. $10,000.00 will be made available annually for a number of years to make a study of rheumatism.

Dr. John C. Ruddock (Fellow), Los Angeles, addressed the 34th annual meeting of the Nevada State Medical Association, during September, on "Peritoneoscopy, Technic and Clinical Experiences."

Dr. Warren C. Breidenbach (Fellow), Dayton, has been appointed a member of the Ohio Public Health Council.

Dr. Carl V. Weller (Fellow), Professor of Pathology, University of Michigan Medical School, Ann Arbor, delivered a series of postgraduate lectures in Lima, Ohio, September 20 to 24. The subjects included constitutional types in relation to disease; developmental disturbances of the face, mouth and neck; pathology of coronary occlusive disease, the thyroid gland, the gallbladder and the kidneys; parasitic worms of the North Central States; endometriosis; Antony von Leeuwenhoek and his microscopes.

Dr. Thomas T. Sheppard (Associate), Pittsburgh, is a member of the committee appointed to supervise a trust fund of a million dollars given by Miss Emily Renziehausen to the Children's Hospital of Pittsburgh for "Perpetual research in the causes, treatment and cure of diabetes in the youth of the Pittsburgh area."

The first income from the fund is to be used in building an addition to the hospital to be known as the "Renziehausen Memorial Ward and Clinic." In addition to the fund, Miss Renziehausen donated an eleven-acre farm as a site for a home for convalescent children. Any part of the fund not needed for work on diabetes may be devoted to other research work or hospital service.

Dr. Frank L. Roberts (Fellow), Trenton, Tenn., has been given charge of a newly established department of preventive medicine at the University of Tennessee School of Medicine. The department will be jointly supported by the University, the State Department of Health and the Tennessee Valley Authority.

Dr. Roberts will have the title of Professor of Preventive Medicine. He is a graduate of the University of Minnesota Medical School, 1922, was Health Officer of Gibson County from 1924 to 1928, Director of local health service in West Tennessee for the State Health Department from 1928 to 1930 and Director of Health Demonstrations for the Commonwealth Fund in Gibson County from 1930 to date.

Dr. Ernest S. Mariette (Fellow), Oak Terrace, Minn., Dr. J. Burns Amberson, Jr. (Fellow), New York City, Dr. D. O. N. Lindberg (Fellow), Decatur, Ill., and Dr. Paul P. McCain (Fellow), Sanatorium, N. C., participated in the conduct of a symposium on sanatorium administration as a part of the program of the Mississippi Valley Conference on Tuberculosis and the Mississippi Valley Sanatorium Association, Dayton, Ohio, September 22 to 25.

OBITUARIES

DR. HENRY ROBERT MURRAY LANDIS

Dr. Henry Robert Murray Landis (Fellow), a cultured, scholarly citizen and a distinguished, justly celebrated and highly esteemed physician of Philadelphia, died on September 14, 1937.

Dr. Landis was not only an expert clinician and a much sought after consultant but, in addition, he was a skilled and impressive teacher of medical art, a talented author and a recognized authority upon the diseases of the chest. In recent years Dr. Landis has been seriously incapacitated by a chronic, complicated and distressing malady, and his death proved a welcome release from the vicissitudes of an intolerable existence from which the joy of living had long since departed. To those fully aware of the devastating and hopeless illness that he suffered, information that nature's final and infallible panacea, merciful endless sleep, had come to Dr. Landis could only be greeted with a sigh of relief.

Dr. Landis was known to his intimates as "Bob," "H.R.M.L.," or "Hiram," and the number of his admirers, both in and out of the profession, was legion. There will be many a sigh of heartfelt regret from colleagues, friends, patients and former students that such a kind and helpful physician should have become the victim of a relentless and pitiless fate.

H. R. M. Landis was born in Niles, Ohio, in 1872. He was the son of Henry Gardner Landis, M.D. (1848–1886), who was born in Philadelphia, attended Yale University, where he received an A.M. degree in 1867, graduated from the Jefferson Medical College in 1870, served as an intern in the Philadelphia General Hospital (Old Blockley), entered practice in Niles, Ohio, and, a few years later, removed to Columbus, Ohio, where he became Professor of Obstetrics in the Starling Medical College. "Bob" Landis spent his childhood in Ohio, but secured his academic training at Amherst College, graduating with Calvin Coolidge in 1894. Following the example of his father, Landis attended the Jefferson Medical College and received his

degree in 1897. Again in his father's professional footsteps, he served his internship at the Philadelphia General Hospital, where he early revealed his talents and capabilities as an investigator, observer, clinician, reporter and literary critic.

Dr. Landis inherited a love for the best literature and from his school days onward he was recognized as a scholar of distinction. The love of literature and the appreciation of the arts proved a wonderful escape from tedious realities when the ill fortune of illness came.

At the completion of his internship Dr. Landis established his practice in Philadelphia and at once became actively associated with the Medical Department of the Jefferson Medical College and Hospital. In this institution Dr. Landis came in contact with J. Chalmers Da Costa, Hobart A. Hare and other physicians who both intellectually and in medical science stimulated and inspired him. An active service in the dispensaries supplied his inquiring mind with clinical problems and he found himself busied with both teaching and practice.

In 1903 Dr. Lawrence F. Flick, the Nestor of American workers in the field of tuberculosis, was instrumental in incorporating and directing the Henry Phipps Institute for the Study, Treatment and Prevention of Tuberculosis. Dr. Landis was fortunate enough to be selected, with Dr. Joseph Walsh, to take an active part in directing the studies, clinical and sociological, of this useful and justly celebrated organization.

The White Haven Sanitarium for Tuberculosis (Luzerne County, Pa.), another organization of Dr. Flick's judicious planning, was fortunate enough to enlist the enthusiastic coöperation of Dr. Landis, and for thirty years he gave to the patients of this hospital his skilled and efficient services. Dr. Landis was attending physician to the Department for Tuberculosis of the Philadelphia General Hospital for a number of years and resigned this position only when forced to do so by the stress of other duties. When the Henry Phipps Institute became a part of the University of Pennsylvania School of Medicine, Dr. Landis became the Director of the Clinical and Sociological Departments. At this time, 1912, Dr. Landis became the Professor of Clinical Medicine in the University of Pennsylvania School of Medicine, and occupied this position until his death.

In 1917, in collaboration with Dr. George W. Norris, Dr. Landis published a textbook, "Physical Diagnosis and Diseases of the Chest." The text, which entered its fifth edition in 1933, has been justly praised as the best single volume upon its subject matter. The book is used in scores of medical schools and is a volume that is read alike by student, consultant and general practitioner.

Dr. Landis was elected to Fellowship in the College of Physicians of Philadelphia in 1904 and has been an active and interested Fellow in all that organization's activities. The American College of Physicians elected Dr. Landis to Fellowship in 1926. Unfortunately the state of his health prevented Dr. Landis from meeting with the Fellows of the College as he would

have enjoyed doing. He was a member of the Association of American Physicians, the American Climatological and Clinical Association, the National Tuberculosis Association, the American Sanitarium Association and many other organizations.

Dr. Landis was honored by his Alma Mater, Amherst College, in 1929, by being awarded the honorary degree of Doctor of Science. He is survived by his wife, Margaret Tucker Landis, whom he married in 1902.

The College has lost a distinguished Fellow, the medical world a clinician of exceptional ability and the poverty stricken tuberculous an interested and practical sociologist.

E. J. G. Beardsley, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. JOSEPH SAMENFELD

The death of Dr. Joseph Samenfeld, of Brooklyn, N. Y., occurred abroad on September 5, 1937, at the age of 61 years.

Dr. Samenfeld was born in Brooklyn, and after attending public schools, he attended the Pratt Institute and the New York Preparatory School, before entering the University and Bellevue Hospital Medical College from which he graduated in 1903. Dr. Samenfeld was for many years Chief of the Medical Clinic of the Jewish Hospital; Assistant, Associate and Attending Physician, St. Catherine's Hospital; Attending Physician, Greenpoint Hospital; Consulting Physician, Williamsburg Maternity and Lutheran Hospitals; Member, Kings County Medical Society, New York State Medical Association, Williamsburg Medical Society, the American Medical Association and a Fellow of the American College of Physicians since 1923.

Dr. Samenfeld volunteered for service in the World War and was commissioned a captain in the U. S. Medical Corps. He received a congressional medal for distinguished services. He is survived by a twin brother and six sisters.

The community and the profession have lost in Dr. Samenfeld an untiring, diligent worker.

C. F. Tenney, M.D., F.A.C.P.,
Governor for eastern New York